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Exercise for People with Inflammatory Peripheral Neuropathy

Stockley, Rachel

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Exercise for People with Inflammatory Peripheral Neuropathy

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King's College London

United Kingdom

2013

Submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy to
King's College London

Abstract

The overall purpose of this thesis was to examine the role of exercise in people with stable Peripheral Neuropathies (PN). A 12 week community based unsupervised exercise intervention in 16 people after Guillain-Barré syndrome (GBS) or with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and ten healthy controls demonstrated that the exercise intervention was well tolerated and acceptable. After the intervention, PN participants had significantly reduced activity limitations, participation restrictions and fatigue; these improvements were maintained at six month follow up.

Some outcome tools used in the exercise study, demonstrated limitations and so three studies to modify and evaluate tools for assessing mobility and activity limitations were conducted. The results showed that the Walk-12, a walking questionnaire, and the modified Physiological Cost Index, which measures the energy used whilst walking, were valid for use in people with PN. However, whilst the modification to the Overall Disability Sum Score to form the Overall Neuropathy Limitations Scale resulted in greater sensitivity and face validity, its responsiveness was somewhat reduced.

The fatigue profile of 13 people with PN was described and compared to healthy people, to identify potential contributors to fatigue. Despite significantly greater experienced fatigue, PN participants did not have abnormal muscle fatigue. However, the experienced fatigue was significantly associated with greater activity limitations and poorer functioning in PN participants and they had significantly reduced cardiovascular fitness, were weaker and less active than healthy participants.

Although there are several limitations of the studies in this thesis, they indicate that exercise was practical and may be helpful in reducing activity limitations and fatigue in people with PN. The results also identify outcome tools to evaluate functioning and provide data to inform the development of a controlled trial to evaluate the efficacy of exercise to manage activity limitations and fatigue in people with PN.

Declaration

I hereby declare that all the work contained in this thesis is my own. The contribution of others to aspects of this work has been described and recognised in the relevant sections.

A handwritten signature in black ink, appearing to be 'RCS', followed by a period.

Signed:.....

Date:.....13.09.2013.....

Rachel C Stockley

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List of Abbreviations

ADCB	Activity dependent conduction block
ADL	Activity of daily living
AI	Ambulation Index
AIDP	Acute inflammatory demyelinating polyradiculoneuropathy
AMAN	Acute motor axonal neuropathy
AMSAN	Acute motor and sensory axonal neuropathy
BDI	Beck depression inventory
BI	Barthel Index
CIAP	Chronic idiopathic axonal polyneuropathy
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CMT	Charcot-Marie-Tooth disease
CNS	Central Nervous System
DADS	Distal acquired demyelinating symmetrical neuropathy
DLFR	Delayed low frequency recovery
EADL	Extended activities of daily living
EMG	Electromyography
EO ₂	Oxygen cost
FAC	Functional Ambulation Category
FIM	Functional Independence Measure
FI	Fatigue index
FIS	Fatigue impact scale
FLP	Functional limitations profile
FQ	Fatigue Questionnaire
FSS	Fatigue severity scale
GBS	Guillain-Barré Syndrome
GBSSG	Guillain-Barré Syndrome Support Group
HADQI	Health assessment questionnaire disability index
HADS	Hospital Anxiety and Depression scale
HAP	Health activity profile

HHD	Hand held dynamometry
HMSN	Hereditary motor and sensory neuropathy
HR	Heart rate
ICC	Intra class correlation coefficients
ICF	International classification of functioning
ICIDH	International classification of impairments, disability and handicap
IQR	Interquartile range
MADSAM	Multifocal acquired sensory and motor neuropathy
MCS	Mental component summary score on the SF-36 questionnaire
MFI	Multidimensional Fatigue Inventory
MHC	Myosin Heavy Chain
MMN	Multifocal motor neuropathy
mPCI	Modified physiological cost index
MRC	Medical research council
MS	Multiple sclerosis
MSWS-12	Multiple sclerosis 12 item walking scale (Walk-12)
MVC	Maximal voluntary contraction
N	Newton
nEMG	Normalised electromyography
ODSS	Overall disability sum score
ONLS	Overall neuropathy limitations scale
PCI	Physiological cost index
PCS	Physical component summary score on the SF-36 questionnaire
PDN	Paraproteinaemic demyelinating neuropathy
PFS	Revised Piper fatigue scale
PN	Peripheral neuropathies
PNF	PN participants who reported severe experienced fatigue
PNN	PN participants who did not report severe experienced fatigue
RCT	Randomised controlled trial
RF	Rectus femoris

RHS	Rotterdam handicap scale
RLM	Role limitation due to emotional problems subscale of the SF-36 questionnaire
RLP	Role limitation due to physical problems subscale of the SF-36 questionnaire
RM	Repetition Maximum
RMI	Rivermead Mobility Index
RMS	Root mean square
R-ODS	Rasch built Overall Disability Scale
RPE	Rate of perceived exertion
SD	Standard deviation
SDD	Smallest detectable difference
SE _m	Standard error of the measurement
sEMG	Surface electromyography
SF-36	Short form 36 item questionnaire
SRM	Standardised response mean
TER	Torque EMG ratio
VL	Vastus Lateralis
VM	Vastus medialis
VO ₂	Oxygen consumption
Walk-12	12 item walking scale questionnaire

Publications¹

Graham, R.C., Smith, N.S., White, C.M. The reliability and validity of the physiological cost index of walking in health participants when walking on two tracks. *Arch Phys Med Rehabil* 2005 Vol. 86, p. 2041-2046

Graham, R.C., Smith, N.S. White, C.M. An investigation of the physiological cost index of walking. *Abstract*, International Society for Posture and Gait Research proceedings. Gait and Posture. 2005 Vol. 21, S1; S147

Graham, R.C., Smith, N.S. White, C.M. The reliability and validity of the physiological cost index on two different tracks. *Abstract Clin Rehabil* 2005 Vol. 19, p 576 -577

Graham, R.C., Hughes, R.A.C. Clinimetric properties of a walking scale in peripheral neuropathy. *Journal of Neurol Neurosurg Psychiatry* 2006 Vol. 77, p 977-979

Graham, R.C., Hughes, R.A.C. A modified peripheral neuropathy scale: the overall neuropathy limitations scale. *Journal of Neurol Neurosurg Psychiatry* 2006 Vol. 77, p 973-976

Graham, R.C., Hughes, R.A.C, White, C.M. A prospective study of physiotherapist prescribed community based exercise in inflammatory peripheral neuropathy. *J Neurol* 2007 Vol. 254 p 228-235

Graham, R.C., White, C.M. Subjective and muscular fatigue in people with peripheral neuropathy. *Abstract Physiotherapy* 2007 Vol. 93 Supplement 1, p S124

Graham, R.C., White, C.M. Fatigue report, activity, cardiovascular fitness and energy cost in people with peripheral neuropathy. *Abstract Physiotherapy* 2007 Vol. 93 Supplement 1, S128

Prizes and Awards

King's College London 2003 Postgraduate Symposium Best Poster

Society for Rehabilitation Research Verna Wright Prize 2004 Best poster presentation

King's College London 2005 Postgraduate Symposium Best Oral Presentation

Manchester Metropolitan University 2007 Promising Researcher award

Chartered Society of Physiotherapy 2007 Robert Williams Travel Award

¹ Published under my maiden name of Graham

Chapter 1. Introduction

1.1. Summary

The overall purpose of the thesis was to examine the role of exercise in people with Peripheral Neuropathies (PN). Two aims were developed to meet this objective: (i) to evaluate the practicality and possible effects of a community based exercise intervention for people after Guillain-Barré syndrome (GBS) and with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and (ii) to investigate and describe the nature of experienced and physiological fatigue in people with inflammatory PN.

This chapter provides a background to the aims of this thesis by describing PN and discussing the common problems experienced by people with these conditions. The evidence evaluating the potential role of exercise to manage activity limitations is critically considered to place this thesis in a broader context and to outline the deficits of the current evidence base in PN.

This chapter also describes the nature of fatigue experienced by many people with PN and defines experienced and physiological fatigue. A review of the literature which investigates fatigue in PN is undertaken and the need for further investigation of the contributors to fatigue is highlighted. The chapter closes with a critical discussion of the outcome tools that were used to capture key aspects of functioning in the studies in this thesis.

1.2. Brief Background

Peripheral neuropathies (PN) encompass a range of disorders of the peripheral nerves. In the UK, PN affect approximately 2.4% of the population and commonly produce symptoms of altered sensation, pain and weakness (Martyn and Hughes 1997). There are many forms of PN, but the work in this thesis predominantly focuses upon inflammatory, immune mediated PN. Inflammatory PN have acute forms, including Guillain-Barré syndrome (GBS) and its variants, and chronic forms, including chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and paraproteinaemic demyelinating neuropathies (PDN). These neuropathies are described in Section 1.5.

Immunomodulatory treatments are effective in GBS and can improve chronic PN but are not always curative (Hughes et al. 2006; van Schaik et al. 2002; van Schaik et al. 2005). At least a quarter of patients after GBS or with CIDP have significant sequelae many years after the onset of symptoms (Bernsen et al. 2002; Bernsen et al. 2005; Gorson et al. 1997; Kuwabara et al. 2006). Persistent residual problems, including increased feelings of fatigue, muscle weakness, reduced proprioception and altered sensation contribute to activity limitations and restricted participation in people with PN (de Jager and Minderhoud 1991; Erdmann et al. 2005; Merkies et al. 2002a; Richardson et al. 2001; Teunissen et al. 2000). These activity limitations remain despite standard medical treatment, suggesting that rehabilitative interventions such as exercise warrant examination.

1.3. Aims and Objective

The overall objective of this thesis was to examine the role of exercise for treating people with PN. Therefore, the specific aims of this thesis were to:

- (i) Evaluate the practicality and possible effects of a community based exercise intervention for people at least 12 months after the nadir of Guillain-Barré syndrome (GBS) and people with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) which has been stable for over six months.
- (ii) Investigate and describe the nature of experienced and physiological fatigue in people with inflammatory PN.

1.4. Structure of this thesis

This thesis is structured predominantly chronologically.

This Chapter begins by describing the PN encountered in the studies in this thesis with their management and identifies the common activity limitations experienced by many people with PN. The current literature evaluating exercise in PN is critically considered and the nature of fatigue experienced by many people with PN is described. This chapter concludes with a critical review of the outcome tools that were used in the studies in the thesis.

The study in Chapter Two describes the practicality and possible effects of a 12 week community based exercise intervention for people with PN and evaluates the performance of the tools used. Several outcome tools that were used in this study did not perform as well as anticipated. The observed limitations of the primary outcome tool, the Overall Disability Sum Score (ODSS) were addressed by adapting it to produce a new tool, the Overall Neuropathy Limitations Scale (ONLS). The evaluation of the reliability, validity and responsiveness of the ONLS in comparison to the ODSS is presented in Chapter Three.

The findings from Chapter Two also demonstrated that closer examination of tools which indicate aspects of mobility was warranted. Therefore, the properties of the Physiological Cost Index (PCI) and a mobility questionnaire, which had not previously been used in PN (Walk-12) were investigated in Chapter Four.

In Chapters Five and Six, the nature of fatigue experienced by some people with PN is described and a range of potential contributors to fatigue in people with PN, such as strength, physiological fatigue and activity levels, are investigated.

The key findings of the studies are summarised in Chapter Seven and the implications for clinical practice and future research in context of the studies in this thesis are discussed.

1.5. Peripheral neuropathies

Common symptoms of peripheral neuropathies include weakness, sensory changes and pain. Peripheral neuropathies can be hereditary or produced from toxin exposure, nutrient deficiencies, vasculitis, mechanical compression, neoplasms, metabolic disorders (e.g. diabetes), infection and inflammation (Goetz, 2007). They can also be classified depending upon the patterns of symptoms they produce. They can affect single nerves (mononeuropathy), several nerves (multiple mononeuropathy), a single nerve root (radiculopathy), several (polyradiculopathy), a nerve plexus (plexopathy) or can be generalised (symmetrical polyneuropathy) (Hughes 2002b; Thomas 1970).

Community dwelling, population based studies have reported the prevalence of symmetrical polyneuropathies to be between 2400 and 7000 per 100,000 (Martyn and Hughes 1997). In Europe, diabetic neuropathy is the most common form of symmetrical polyneuropathy and affects over half of people with diabetes (Hughes 2002b; Vinik et al. 2000). Polyneuropathies are also reported in up to a quarter of people who abuse alcohol (Martyn and Hughes 1997; Vittadini et al. 2001).

Some neuropathies are characterised by the presence of inflammation and have acute forms, notably GBS, and chronic variants such as CIDP (Hughes 2002b). Guillain-Barré syndrome is perhaps the most well recognised inflammatory symmetric neuropathy. Although its incidence is moderately low (one to two people per 100,000), it is the most common cause of flaccid paralysis in Western countries (Govoni and Granieri 2001; Hovi and Stenvik 2000; Martyn and Hughes 1997).

Chronic inflammatory demyelinating polyradiculoneuropathy is one of several chronic symmetric peripheral neuropathies, which are characterised by a gradual development of weakness and altered sensation. It is estimated to affect three people per 100,000 (Martyn and Hughes 1997).

People after GBS or with CIDP were chosen as the predominant patient groups to be studied in this thesis, as despite some clinical differences, both produce similar, significant and persistent activity limitations which appear refractory to medical treatment, but might be improved by rehabilitative interventions. The pathophysiology, management and outcome of these conditions are discussed in Sections 1.6 and 1.7.

Despite the relatively low prevalence of inflammatory symmetric neuropathies, the host institution for this PhD had a special interest in these conditions, making recruitment of sufficient numbers of participants feasible and providing a unique opportunity for investigation.

Diabetic PN was not included as although it is more common, the neuropathy is secondary to a primary metabolic disorder, predominantly affects sensory nerves and the benefits of exercise and activity are already relatively well researched in this patient group (Thomas et al. 2006). Other chronic peripheral neuropathies including PDN, CMT and CIAP were included in some studies in this thesis and so are outlined in Sections 1.8.1, 1.8.2 and 1.8.3. Participants

with these conditions were included as they demonstrated similar activity limitations to people with inflammatory PN and increased the external validity of the results.

1.6. Guillain-Barré syndrome

Guillain-Barré syndrome is an immune mediated PN (Hughes and Cornblath 2005). It was named for two of a trio of French doctors, Guillain, Barré and Strohl, who, in 1916, reported two cases of acute weakness in infantrymen (Asbury 1990; Hughes 1990). They described features which today are considered typical of the disease, namely symmetrical sensory alterations, muscle weakness and loss of deep tendon reflexes, and increased protein in the cerebrospinal fluid (Hughes 1990). Other features include cranial nerve involvement and autonomic dysfunction including tachycardia, other potentially serious arrhythmias, hypo- or hypertension and vasomotor symptoms (Asbury and Cornblath 1990).

Guillain-Barré syndrome is characterised by rapidly worsening symptoms which progress for up to four weeks, before plateau and eventual improvement (Asbury and Cornblath 1990). A typical plateau phase lasts from one to four weeks (Asbury and Cornblath 1990; Hughes 1990), but recovery may not start for several months and is often incomplete (Hughes 1990; Nicholas et al. 2000).

There appears to be a bimodal distribution for age of onset in younger patients and in the elderly, although this is controversial (Govoni and Granieri 2001). Approximately two thirds of patients with GBS report symptoms of an infection several weeks before the onset of weakness or sensory alterations (Asbury and Cornblath 1990; Hughes 1990; Jacobs et al. 1998). These infections appear to initiate an aberrant immune response against peripheral nerves and result from cross reactivity between antibodies or T-cells to the infective agent and myelin or axonal antigens (molecular mimicry) (Ang et al. 2004; Gabriel et al. 2000; Hartung and Toyka 1990; Hughes and Cornblath 2005). *Campylobacter jejuni* (*C. jejuni*) infection, usually causing enteritis, is the most common antecedent infection, and was evident in 32% of patients (49 from 154) with GBS in one study (Jacobs et al. 1998). Despite this, only one in 1000 cases of *C. jejuni* will lead to development of GBS which suggests that other factors, including genetics or previous exposure to an infective agent, determine who develops GBS (Quarles and Weiss 1999).

1.6.1. Subtypes of Guillain-Barré syndrome

Guillain-Barré syndrome has several widely recognised forms which are delineated by neurophysiological testing and the pattern of symptoms (Asbury et al. 1969; Hughes et al. 1999). Those that produce limb weakness are considered in this thesis and so discussed here.

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common form of GBS in the West and accounts for at least 85% of all cases (Rees et al. 1995). Symptoms include progressive weakness, often accompanied by sensory deficits and signs of autonomic dysfunction (Hartung 1998). Clinical tests demonstrate elevated protein in the cerebrospinal fluid, and nerve conduction studies show multifocal slowing of conduction velocity and partial

conduction block (Cornblath 1990; Hartung et al. 2002; Hughes et al. 1999). The pathogenesis of AIDP has not been fully elucidated. According to one hypothesis based upon an animal model of experimental autoimmune neuritis, a T-cell response against one of the myelin proteins P0, P2 or PMP22 (Gabriel et al. 2000) results in penetration of the peripheral nerve and spinal nerve roots by activated lymphocytes and macrophages which demyelinate segments of the nerve (Hadden et al. 2001; Pritchard and Hughes 2004).

Acute motor axonal neuropathy (AMAN) is a much less common variant of GBS in Western countries (Hadden et al. 1998; Visser et al. 1995). These patients have only motor symptoms, with no sensory involvement (Hafer-Macko et al. 1996). A targeted attack against specific GM1 gangliosides has been linked to the characteristic selective motor axon damage (Chowdhury and Arora 2001; Hadden et al. 1998). This form of GBS is more common in Asia, especially during the summer months, and accounts for over 70% of GBS cases in China (Ho et al. 1997). However AMAN was only present in 27 of 147 European patients with GBS (18%) (Visser et al. 1995).

A third variant of GBS is characterised by sensory and motor deficits caused by axonal damage to the sensory and motor nerves. This produces acute motor and sensory axonal neuropathy (AMSAN) (Chowdhury and Arora 2001; Feasby et al. 1986). Similarly to AMAN, it occurs in fewer people than AIDP in Europe and America and axonal damage is caused by a targeted immune attack on gangliosides, but in this case, present in both sensory and motor nerves (Chowdhury et al. 2001).

1.6.2. Management of Guillain-Barré syndrome

The aim of acute medical treatment in GBS is to limit the damage caused by the aberrant immune response and to provide supportive care (Hughes et al. 2005). Plasma exchange or intravenous immunoglobulin are used in over 65% of cases (Cheng et al. 2000; Chio et al. 2003; Rees et al. 1998) and appear to accelerate recovery, reduce residual activity limitations and accelerate improvements in walking ability (Hughes et al. 2006; Raphael et al. 2002).

Most natural recovery occurs within the first year after GBS for the majority of people (Forsberg et al. 2004). For those severely affected, clinical recovery can extend to two years (de Jager and Minderhoud 1991) but, in longer term studies, nearly all patients report no further change after three years (Bersano et al. 2005). Several factors predict a poor outcome at one or two years after the onset of GBS. These include increased age at onset, severe weakness at nadir, inexcitable nerves and diarrhoea preceding *C. jejuni* infection (Chio et al. 2003; Fletcher et al. 2000; Rees et al. 1995; Van Koningsveld et al. 2007).

Rehabilitation appears important during recovery after GBS but the components of rehabilitative treatment are likely to be highly individual and have not been detailed in many studies. Physiotherapeutic interventions for people with PN may include maintenance of joint range, timely management of secondary complications, re-education of movement and strength, provision of assistive devices to maximise function and improvement of overall fitness (Herbison et al. 1983; Hughes et al. 2005; Karni et al. 1984; Lennon et al. 1993;

Nicholas et al. 2000). Two small, uncontrolled studies have also described benefit from novel interventions using partial body weight support and mechanised balance training (Bulley 2003; Tukey and Greenwood 2004). Although the content of rehabilitation treatments was not described, a longer duration of rehabilitation was shown to be significantly associated with improved scores on functional outcome tools, including the Barthel index, in a longitudinal study of 24 people with GBS over three years (Nicholas et al. 2000). However, in a study of ten people 11 to 35 months after the onset of GBS, the duration of treatment varied enormously and five participants had their therapy withdrawn despite contractures and significant activity limitations (Lennon et al. 1993).

1.6.3. Outcome after Guillain-Barré syndrome

Despite timely treatment and rehabilitation, persistent symptoms of GBS may be present several years after nadir and are estimated to affect almost half of all patients (Cheng et al. 2000; Dornonville de la Cour and Jakobsen 2005). This estimate increased to 65% (n= 37) in those who were most severely affected by GBS and required ventilation at nadir (de Jager and Minderhoud 1991). Residual problems after GBS include alterations in sensation and proprioception, decreased muscle strength, reduced walking ability and increased feelings of fatigue (Dornonville de la Cour and Jakobsen 2005; Merkies et al. 1999). Autonomic function is reported to return to normal in the majority of people after one year (Flachenecker et al. 1997), but reduced muscle strength is reported in over half and sensory deficits are evident in more than two thirds of people at least one year after GBS (Bernsen et al. 2001; Forsberg et al. 2004; Hughes and Cornblath 2005). Persistent activity limitations caused significant alterations in the lives of people after GBS. A small number did not regain the ability to walk (4% of 79) whilst between seven (of 42) to 20% (of 53) required walking aids and 17% (of 79) were unable to run one to two years after nadir (Cheng et al. 2000; Dornonville de la Cour and Jakobsen 2005; Forsberg et al. 2004; Forsberg et al. 2005; Rees et al. 1998). Two years after GBS, 37% of 57 patients could not perform at their previous physical level (de Jager and Minderhoud 1991) and between 12% (of 42) and 27% (of 70) were dependent in some activities of daily living (Bernsen et al. 2002; Bersano et al. 2005; Forsberg et al. 2005). This necessitated retirement or changing jobs in 17% (of 42) to 38% (of 122) (Bernsen et al. 2002; Bernsen et al. 2005; Bersano et al. 2005; de Jager and Minderhoud 1991). Between 44% (of 122) and 54% (of 90) reported altering hobbies as a direct result of their health two years after GBS, often reducing the intensity and frequency of physical and social activities (Bernsen et al. 2002; Bernsen et al. 2005; Lennon et al. 1993). This suggests that return to or uptake of exercise cannot be assumed to be practical or achievable for some people with PN.

Whilst decreased muscle strength, altered sensation and decreased proprioception contribute to persistent activity limitations, not all limitations have been adequately explained by these impairments (Bernsen et al. 2005; Lennon et al. 1993; Merkies et al. 2003b). Despite strength and sensation recovering to near normal values, many people have reported difficulty returning to pre morbid levels of functioning (Bersano et al. 2005; Burrows and Cuether 1990; Lennon et al. 1993). This indicates that other factors must contribute to reduced functioning (Bernsen et

al. 1997; Dornonville de la Cour and Jakobsen 2005; Lennon et al. 1993). One of these factors could be severe experienced fatigue which has been significantly associated with poorer functioning and was reported by over 80% of 113 people with GBS or after CIDP several years after diagnosis (Merkies et al. 1999). However, the factors that contribute to the severity of experienced fatigue require investigation in order to increase understanding and to guide the development of treatments to reduce the negative effects associated with fatigue in people with PN.

1.7. Chronic inflammatory demyelinating polyradiculoneuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is presumed to be an acquired immune mediated disorder which causes demyelination of the peripheral nerves. Damage to the axon can also occur (Bouchard et al. 1999; Koller et al. 2005). It can start at any age and is slightly more common in those over 40 and in men (1.3:1) (Lunn et al. 1999; McLeod et al. 1999).

A definitive diagnostic marker for CIDP has yet to be found (Koller et al. 2005). The typical clinical picture consists of an insidious onset of progressive or relapsing, symmetrical proximal and distal weakness, sensory loss, partial conduction block and reduced conduction velocity with reduced or absent reflexes (Ad Hoc Subcommittee of the American Academy of Neurology AIDS task force. 1991; Hughes et al. 2001; Joint task force of the EFNS and the PNS 2005; Saperstein et al. 2001). In a series of 92 patients, 80% experienced sensory changes and muscle weakness and 16% (of 100) to 24% (of 92) demonstrated involvement of the cranial nerves (Bouchard et al. 1999; McCombe et al. 1987). Crucially, the progression of symptoms of CIDP exceeds two months, distinguishing CIDP from subacute inflammatory demyelinating neuropathy and GBS (Hughes 2002a). Other, less frequent symptoms include sensory ataxia, tremor and autonomic involvement (Bouchard et al. 1999; Hughes 2002a; Lyu et al. 2002; McCombe et al. 1987).

The inflammatory features characteristic of CIDP and its good response to treatments targeting the immune system support the hypothesis that CIDP is caused by an aberrant immune response (Mehndiratta et al. 2004a; van Schaik et al. 2002). A clear association with antecedent infection has not been reported, suggesting that the mechanisms of immune mediated nerve damage differ from GBS (McCombe et al. 1987; Melendez-Vasquez et al. 1997). However, as the onset of CIDP is gradual and may be unnoticed for several months, recollection of antecedent illness can be inaccurate.

Refinement of clinical diagnosis has identified other forms of chronic demyelinating neuropathies which differ from the typical presentation of CIDP, and which may represent distinct diseases (Koller et al. 2005). These forms account for around one tenth of all cases of CIDP (Hughes 2002a). Distal acquired demyelinating symmetric neuropathy (DADS) is distinguished from typical CIDP by the presence of distal sensory or sensorimotor symptoms with little proximal involvement (Katz et al. 2000). An asymmetrical presentation of sensory and motor symptoms is characteristic of another form of CIDP, called multifocal acquired

demyelinating sensory and motor asymmetrical neuropathy (MADSAM) (Saperstein et al. 1999; Van den Berg-Vos RM et al. 2000).

1.7.1. Management of chronic inflammatory demyelinating polyradiculoneuropathy

In CIDP, treatment is directed to manage the immune and inflammatory processes and to limit secondary axonal damage (Joint task force of the EFNS and the PNS 2005; Koller et al. 2005). Corticosteroids are widely used in CIDP (Mehndiratta and Hughes 2001). However, they are not beneficial in pure motor forms of CIDP (Hughes 2002c; Umapathi et al. 2005) and their side effects have led to continued searches for other treatments (Hughes 2002a). Intravenous immunoglobulin and plasma exchange have also been used (Hughes 2002a; Mehndiratta et al. 2004a; van Schaik et al. 2002) but benefits of both are short lived and repeated treatment at regular intervals may be required (Joint task force of the EFNS and the PNS 2005; van Schaik et al. 2002). Other suggested treatments to manage CIDP include immunosuppressants, interferon and autologous stem cell transplantation (Good et al. 1998; Vermeulen and Van Oers 2002) but all these treatments require further investigation to determine their effectiveness.

Supportive treatments for people with CIDP, including adequate pain relief, provision of assistive aids, maintenance of independence and psychological support are recommended (Joint task force of the EFNS and the PNS 2005). Although one study found improvements in functioning in four people with CIDP after they completed a supervised exercise intervention (Garssen et al. 2004; Garssen et al. 2005a), no studies have examined the effects or content of multidisciplinary rehabilitation upon the symptoms of CIDP, either during acute relapses or in the management of chronic activity limitations.

1.7.2. Outcome in chronic inflammatory demyelinating polyradiculoneuropathy

In a series of 46 and 92 patients with CIDP, 43 to 65% followed a relapsing-remitting course (Lunn et al. 1999; McCombe et al. 1987) whilst 13% of 46 patients had a monophasic illness (Lunn et al. 1999). Conversely, a chronic progressive course with gradual worsening was reported in approximately 37% (of 46) (Lunn et al. 1999) and up to 40% (of 38) of patients required regular immunomodulatory treatment five years after their initial treatment began (Kuwabara et al. 2006). In one study, 11% of 83 patients had died within six years of onset as a result of complications associated with CIDP (Bouchard et al. 1999). Several factors predict a poorer outcome, these include advancing age, weakness in all four limbs and axonal damage (Bouchard et al. 1999; Koller et al. 2005; Sghirlanzoni et al. 2000).

At least four years after the onset of CIDP, over 90% of a series of 67 patients exhibited some persistent symptoms (Gorson et al. 1997). These included muscle weakness, altered sensation and pain (Gorson et al. 1997). Many also reported moderate limitations in activities, suggesting that they struggled to return to hobbies and physical activities (Gorson et al. 1997; McCombe et al. 1987). In one study, only 56% (of 47) were independent in all activities of daily

living, six years after the onset of CIDP (Bouchard et al. 1999). In a cross sectional population investigation, based in the South East Thames region, Lunn et al. (1999) reported that a mean of 8.9 years after the onset of symptoms, 13% (of 46) of patients used an aid to walk and required help with activities of daily living. In a smaller study, ten of 12 people with CIDP reported difficulty walking or climbing stairs, although the time since diagnosis was not reported (Erdmann et al. 2005).

The effect of CIDP on wider measures of health, participation and fatigue in this patient group has not been widely investigated. However, in a study of 113 people after GBS or with CIDP Merkies et al. (1999) reported that they had significantly more severe experienced fatigue than healthy participants. Although the severity of experienced fatigue in CIDP participants was not reported separately, this finding indicates that fatigue is likely to be problematic in this patient group.

1.8. Other peripheral neuropathies

1.8.1. Paraprotein associated demyelinating neuropathy associated with monoclonal gammopathy of undetermined significance

Ten per cent of patients with chronic idiopathic neuropathies have an associated monoclonal gammopathy (PDN) (Kissel and Mendell 1995). The clinical picture of PDN is variable but the commonest form comprises slowly progressive, symmetrical distal weakness and sensory changes (Isoardo et al. 2005; Kissel and Mendell 1995). Painful paraesthesiae, ataxia, decreased balance and upper limb tremor are prominent, but autonomic and cranial nerve involvement are rare (Hartung 1998; Kissel and Mendell 1995; Mehndiratta et al. 2004b). Neurophysiological studies show mixed axonal degeneration and demyelination (Kissel and Mendell 1995; Mehndiratta et al. 2004b). After an average of eight years many people have only minor limitations in their activities of daily living (Nobile-Orazio et al. 2000) although no studies have considered quality of life or wider health in this patient group.

1.8.2. Charcot-Marie-Tooth Disease

Charcot-Marie-Tooth (CMT) disease is the most common of the hereditary neuropathies and can have demyelinating or axonal forms. It is estimated to affect from eight to 41 people per 100 000 (Hughes 2002b; Kuhlénbaumer et al. 2002). Type 1 is the most common form, and accounts for approximately 80% of CMT cases. It causes demyelination which can result in a range of symptoms from none to severe sensory and motor loss (Hughes 2002b; Kuhlénbaumer et al. 2002). It is usually caused by duplication of the gene for peripheral nerve protein 22 on chromosome 17.

1.8.3. Chronic idiopathic axonal polyneuropathy

Up to 25% of neuropathies affecting the peripheral nerves have no causative diagnosis, despite detailed investigation (Notermans and Wokke 1996). These idiopathic neuropathies produce slowly progressive axonal damage (Hughes et al. 2004; Notermans and Wokke 1996) and are termed chronic idiopathic axonal polyneuropathies (CIAP). People with CIAP

experience a gradual and insidious onset of distal, predominantly sensory or sensorimotor symptoms, including pain, which tend to be worse in the feet than hands (Hughes et al. 2004; Notermans and Wokke 1996). The disease is more common in those over 50 and in men (Hughes et al. 2004). People with CIAP report reduced walking ability and decreased functioning, including limitations in physical functioning, poor mental health and decreased energy and vitality (Hughes et al. 2004; Teunissen et al. 2000).

1.9. Exercise

1.9.1. Clinical benefits of exercise

Since the time of the ancient Greeks, physicians have advocated exercise to maintain and improve health and function (Berryman 1989). However, traditional medical care has often focussed predominantly upon the prevention and management of impairments in people with physical limitations, giving little attention to health promotion or management of secondary health conditions (Rimmer 2005a). Recent advances in health care have increased overall life expectancy including for those people with persistent activity limitations (Office for National Statistics 2005; Rimmer 2005a), although existing impairments are likely to be compounded by the natural aging process (McDonald 2002). People with impairments and activity limitations could be predisposed to a sedentary lifestyle that can increase their risk of developing secondary health complications such as heart disease, obesity and poor mental health (Gordon et al. 2004; Rimmer 2005a). As people with PN experience persistent activity limitations and restricted participation they may also be at risk of these health complications although this has not been studied (Gorson et al. 1997; Lennon et al. 1993; McDonald 2002).

Physical activity is considered to be any bodily movement that is produced by voluntary muscles and consumes energy (Caspersen et al. 1985) and is associated with reductions in all-cause mortality and in the incidence of coronary heart disease and osteoporosis (Atlantis et al. 2004; Bean et al. 2004). Exercise is a subset of physical activity and has been defined as “a planned or structured activity which aims to improve or maintain physical fitness” (Caspersen et al. 1985, p126). There is strong and consistent research demonstrating that regular exercise has a protective effect against diseases associated with a sedentary lifestyle, reducing morbidity and mortality (Brach et al. 2004; Kesaniemi et al. 2001; Oguma et al. 2002; Villeneuve et al. 1998). Exercise can also improve daily functioning and has demonstrated beneficial effects beyond physiological parameters, including improvements in quality of life and feelings of well-being (Fox 1999; Rimmer et al. 2004).

Potentially, these benefits could be replicated in people with PN if they were able to exercise regularly. However, difficulty accessing appropriate services, fear and lack of support mean that few people with restricted functioning engage in physical pursuits (Rimmer 1999; Rimmer et al. 2004; Rimmer 2005b). The location of exercise programmes may also affect the ability of people with activity limitations to participate (Rimmer et al. 2004). Whilst a centre based and medically supervised programme would provide support and motivation to exercise, potential volunteers who have difficulties travelling may not be able to participate and the cost of continual medical supervision may prove prohibitive for healthcare providers. Programmes based in the community or in the home are more practical, facilitate regular exercise and produce higher adherence (Ashworth et al. 2005; King et al. 1991; Rimmer et al. 2004), but medical supervision of exercise in this setting would be extremely difficult. Some people with PN may find exercising effectively difficult without supervision, could be unwilling to exercise in public (for instance in a gym) or be fearful of exercising alone, and are at risk of injuries

secondary to muscle weakness, loss of proprioception and balance deficits. However, they may be encouraged to participate in an exercise programme if it is shown to be practical and is prescribed and supported by health professionals. This highlights the need to investigate the practicality and acceptability of an unsupervised community based programme in people with inflammatory PN.

In the following sections, the evidence evaluating exercise in neurological conditions is summarised, followed by detailed consideration of exercise in PN.

1.9.2. Exercise interventions in neurological conditions

Exercise interventions in neurological groups have been shown to be beneficial for reducing impairments such as muscle weakness (Duncan et al. 1998; Mostert and Kesselring 2002; Oken et al. 2004; Petajan et al. 1996; Teixeira-Salmela et al. 1999; White et al. 2004). They have also improved aspects of activities and participation (Petajan et al. 1996; Teixeira-Salmela et al. 1999), although this has not been found in all studies and depends upon the type of exercise used (Meek et al. 2003).

In neurological conditions affecting the central nervous system (CNS), including stroke and multiple sclerosis (MS), regular exercise has been reported to reduce impairments and minimise activity limitations in several studies (Killeff and Ashburn 2005; Leroux 2005; Liu et al. 2003; Marigold et al. 2005; Oken et al. 2004; Surakka et al. 2004; Teixeira-Salmela et al. 1999; White et al. 2004). A systematic review of exercise for people after stroke identified 24 randomised controlled trials (RCT) that met the inclusion criteria, comprising 1147 participants (Saunders et al. 2009). The synthesis of the results was limited by the lack of common outcome tools and the strength of several studies was reduced as they omitted details of assessor blinding (seven studies), were not blinded (five studies), had selection bias (five studies) or provided greater time and attention to the training group when compared to the control (nine studies). However, the review found that there was consistent evidence that physical training benefited aerobic capacity (peak oxygen consumption, three trials) and mobility (eight trials) although there was insufficient evidence to draw conclusions on the effect of training on activity limitations.

A systematic review of nine controlled trials of exercise comprising a total of 260 patients with MS concluded that exercise therapy appeared to increase muscle power, exercise tolerance and mobility related activities of daily living (Rietberg et al. 2005). Pooling of data was not possible due to the range of outcome tools used so conclusions were based on a qualitative best evidence synthesis which considerably decreases their strength (Rietberg et al. 2005). Furthermore, there was a high risk of bias as only two studies stated that they blinded assessors and the sample sizes in each of included studies were small. However, exercise was based in the community and was not always supervised, which suggests that this form of exercise could also be practical and have some benefit for people with PN.

Exercise interventions in neuromuscular conditions are also reported to improve functioning (Aitkens et al. 1993; Dean and Ross 1991; Wright et al. 1996). However, these studies are

generally of lower methodological quality than those in conditions affecting the CNS as they utilise smaller samples, lack blinding and are not adequately controlled. A systematic review including only two studies comprising 52 people with amyotrophic lateral sclerosis or motor neuron disease reported that strength training benefited activities of daily living (ADL). However, this was based on the findings of two small studies so the strength of these conclusions is limited (bello-Haas et al. 2008). A review of strength training for people with muscle disease identified three studies of 121 people with either myotonic dystrophy, facioscapulohumeral muscular dystrophy or mitochondrial myopathy. Although there was insufficient evidence of any benefit, the results showed that training did not appear harmful (Voet et al. 2009).

Whilst the differences in pathophysiology, signs and symptoms of these conditions to PN mean that these findings cannot be extrapolated to PN, these studies provide background to, and some support for, the investigation of exercise in people with inflammatory PN.

1.9.3. Exercise interventions in peripheral neuropathy

A Cochrane systematic review of exercise for people with PN has been completed (White et al. 2007a). Studies were selected for inclusion in the review if they were randomised or quasi randomised trials, and compared exercise in people with PN to no treatment or an alternative form of treatment. The review also aimed to select trials in which the primary outcome tool measured an aspect of functional ability at least eight weeks after the start of the intervention (White et al. 2007a). From 29 full text articles, only one trial of 29 people with CMT and 33 people with myotonic dystrophy met all criteria for inclusion (Lindeman et al. 1995). Two additional studies were also included despite not measuring outcome beyond six weeks (Richardson et al. 2001; Ruhland 1997). These three studies included 82 participants with inflammatory (25 patients), hereditary (37 patients) or metabolic (20 patients) forms of PN, although only two studies published details of the criteria used to secure diagnoses (Lindeman et al. 1995; Richardson et al. 2001). Each study investigated the effect of different forms of exercise interventions so results could not be considered together. Lindeman et al.'s (1995) study examined the effects of 24 weeks of progressive strength training in 29 people with CMT, Ruhland et al. (1997) investigated the effect of combined aerobic and strengthening exercise over six weeks in 28 people with chronic PN and balance training was evaluated in ten diabetic participants in the study by Richardson et al. (2001).

The methodological design, results and activity limitations of each of these studies are discussed in detail within the training modality sections (Pages 33 to 38). In brief, the findings of two studies which included progressive resistance training demonstrated significantly increased strength in trained muscles in people with CMT (Lindeman et al. 1995) and in those with CIDP and idiopathic neuropathy (Ruhland 1997). They also reported significant improvements in some aspects of physical and functional performance after training (Lindeman et al. 1995; Ruhland 1997). The third study found significant improvements in clinical balance measures in ten participants with diabetic PN who had undertaken three

weeks of balance and distal strength training when compared to an equal number of control participants who trained the upper limbs (Richardson et al. 2001).

All included studies were judged to have inadequate allocation concealment and randomisation as two of the three studies matched participants in control and training groups, introducing a high risk of bias (White et al. 2007a). Lindeman et al. (1995) matched participants in control and training groups on knee extensor strength and performance on a stair climbing task, whilst Ruhland (1997) matched participants on age and gender. One study attempted to blind patients to treatment (Richardson et al. 2001) and one other study stated that they blinded the assessor (Lindeman et al. 1995). Two of the included studies demonstrated significant differences between control and training groups at baseline (Richardson et al. 2001; Ruhland 1997) despite matching control and training groups on age and gender in one (Richardson et al. 2001) and two studies were at risk of bias due to attrition during the study (Lindeman et al. 1995; Richardson et al. 2001).

The results of the included studies indicated that progressive resistance training may benefit muscle strength. However data were not able to be pooled as differing outcome tools were utilised in each study, indicating that suitable and agreed outcome tools are yet to be established or widely used in this patient group. The systematic review concluded that there was insufficient evidence to evaluate the effect of exercise upon functional ability in people with PN and the high risk of bias in the included studies mean that the findings could not be confidently attributed to the effect of exercise (White et al. 2007a). The authors also concluded that a large, well designed controlled trial was needed to provide more evidence of the effectiveness of exercise in PN, but that supporting data was required to inform its design (White et al. 2007a).

1.9.4. Training modalities

Many exercise interventions in health and patient groups utilise strength training, aerobic training, or a combination of the two. Selection of the training modality is informed by the specific aims of exercise and determines the nature of any benefits (American College of Sports Medicine 1995). In the next section, the literature evaluating exercise in neurological conditions, with a specific focus on PN, is critically considered.

Strength training

Many patients after GBS (48% of 40 patients between one and seven years after nadir) or with CIDP (over 90% of 67 patients over two years from the onset of symptoms) display muscle weakness in at least one muscle group (Dornonville de la Cour et al. 2005; Gorson et al. 1997). This may result from incomplete reinnervation of muscle fibres which became denervated during the active neuropathic process (Dornonville de la Cour et al. 2005), but can be exacerbated by disuse (Duchateau and Hainaut 1998).

Progressive resistance training is a common method of increasing muscle strength. It comprises near maximal muscular contraction against a high resistance. According to DeLorme (1945) multiple sets of resistance exercises should be performed in which individuals

lift a load which is equivalent to their ten-repetition maximum (RM). Each individual's training load is determined by finding the maximal load that they can move ten times before temporary failure of the muscle (Fish et al. 2003). Participants begin training by completing sets at a percentage of this load (typically 50% to 75% of 10RM) and the last set of repetitions is performed at 100% of their 10RM. The Oxford system of progressive strength training utilises a similar approach but participants complete the first set of repetitions at 100% of 10RM, and subsequent sets at 75% and 50% (Fish et al. 2003). Both approaches increase the load or resistance as training progresses (Campos et al. 2002; De Lorme 1945; Khouw and Herbert 1998) and have demonstrated similar strength gains (Fish et al. 2003). Strength training utilises the overload principle in which the muscle is subjected to greater loads than normal (Campos et al. 2002; De Lorme 1945; Khouw and Herbert 1998). Strength improvements after training are due to a combination of increased activation of the muscle, improved muscular metabolism, increased stiffness of connective tissues, hypertrophy and possibly hyperplasia of muscle fibres (Moritani 1992) and strength changes demonstrate specificity to the method of training (Baker et al. 1994; Roig et al. 2009). Changes in activation and muscle metabolism occur relatively quickly, but muscle fibre hypertrophy is reported to become apparent after at least four weeks of training in young participants, taking considerably longer in older people, and is dependent upon the training intensity and frequency (Kraemer et al. 2002; Moritani 1992).

Maintenance of muscle strength predicts better function in healthy adults as they age (Brill et al. 2000). In their systematic review of physical fitness training in stroke, Saunders et al. (2009) found only four trials of strength training (n=158) that met the criteria for inclusion but, despite significant strength gains, there was insufficient evidence to show benefits to function (Saunders et al. 2009). In MS, a systematic review of nine studies comprising 260 participants concluded that there was evidence in favour of exercise therapy on muscle power. However, the majority of included studies combined multiple training modalities so it is unclear of the effect of strength training alone and the limitations of this review (discussed on Page 31) means the results were at risk of bias (Rietberg et al. 2005).

In hereditary PN, people with CMT have demonstrated significant increases in strength after training in several studies (Aitkens et al. 1993; Chetlin et al. 2004; Lindeman et al. 1995). In a prospective, double blinded controlled study, 20 people with CMT completed thrice weekly progressive strength training of the knee and elbow extensors and flexors for 12 weeks (Chetlin et al. 2004). Participants initially trained at 40% and 20% of one RM for the knee muscles and elbow muscles respectively increasing to 50% and 30% by 12 weeks. They also increased the number of repetitions from three sets of four repetitions to three sets of 10 repetitions by the end of the programme. After training, they demonstrated significant improvements in timed activities of daily living (sit to stand, sitting up from supine, stair climbing, lift and reach) (Chetlin et al. 2004). Strength improved to become closer to normal population derived values but was not compared to baseline tests (Chetlin et al. 2004).

In another study, which comprised 24 weeks of progressive strength training of the knee extensors and flexors and hip abductors and extensors in 14 people with CMT and 15 participants with myotonic dystrophy, a significantly greater mean strength increase (14%) in the knee extensors of CMT participants was shown compared to non-exercising controls (Lindeman et al. 1995). Participants trained three times a week, using free weights and resistance was increased from 60 to 80% of one RM during training whilst repetitions decreased from three sets of 25 to three sets of 10. After completing the programme, participants reported reduced activity limitations on the Western Ontario Mc Master University Arthritis (WOMAC) Index questionnaire which measures pain (five items) stiffness (two items) and functional limitations (17 items), but the validity of this finding is limited as the WOMAC was not designed to reflect activity limitations due to neurological problems. Analysis of the subgroup of CMT participants (n=14) demonstrated a significantly quicker preferred walking speed over six metres when compared to non-exercising controls and 46% (n=6) reported that they could undertake more activities than prior to the study. In another study, 27 people with progressive neuromuscular disease and 14 healthy controls trained thrice weekly for 12 weeks by undertaking moderate resistance upper limb, lower limb and hand grip exercises on one side of the body using free weights (Aitkens et al. 1993). Both groups demonstrated significant improvements in strength on both trained and untrained sides after the programme, and exercise appeared safe and practical, but the effects of these changes on function were not measured. The presence of significant strength gains in untrained limbs indicated that neural adaptations had occurred but the programme lacked clinical relevance as both sides would be trained in usual practice (American College of Sports Medicine 1995). These findings are also limited as the absence of a non-exercising patient control group and rater blinding mean that the observed changes cannot be attributed to the effect of the intervention.

There are no studies which have examined strength training alone in people with inflammatory PN. It seems logical to include strength training in exercise programmes for people with inflammatory PN as it is clear that muscle strength is often reduced (Dornonville de la Cour et al. 2005; Gorson et al. 1997). However, strength training could also have adverse effects (discussed next) resulting in increased weakness which should be considered in the planning and monitoring of an exercise intervention.

Adverse effects of increased muscle activity and strength training

Compensatory reinnervation after denervation results in enlarged motor units (Trojan and Cashman 2005). Enlarged motor units are common in people with after conditions such as polio (Trojan and Cashman 2005), but have also been found in 28 of 37 (76%) people with inflammatory PN by one study (Dornonville de la Cour et al. 2005; Trojan and Cashman 2005). Advice has traditionally warned against strenuous exercise, particularly strength training, in people after polio, suggesting it further reduced muscular strength and function (Johnson and Braddom 1971; Peach 1990). It is postulated that increasing the metabolic demands of enlarged motor units causes premature aging and death of the motor neuron, leading to further

depletion in motor unit numbers and thus increasing muscle weakness (McComas 1998). This could cause late onset of weakness which typifies post polio syndrome and is evident in muscles which were only minimally affected by polio, but have been overused to compensate for more severe weakness elsewhere (Perry et al. 1995).

The effect of reinnervation and exercise on the motor unit has not been directly investigated in people with PN, and no advice regarding strength training in this patient group has been issued. Research in animal models of PN is not conclusive. Some observations in nerve injuries in rats suggest that intense and prolonged activity (such as eight hours of running or electrical stimulation) restricts progressive reinnervation of denervated end plates (Tam et al. 2002; Tam and Gordon 2003). This prevents or reduces the enlargement of motor units after partial denervation and results in incomplete strength recovery (Tam et al. 2002; Tam and Gordon 2003). Conversely, other studies have reported that functional daily exercise was not detrimental to nerve sprouting and recovery immediately after partial denervation in rats (Gardiner and Faltus 1986; van Meeteren et al. 1998). However, this may depend on the type of exercise as 60 minutes of daily treadmill running appeared to retard motor recovery in rats with crushed sciatic nerves but 180 minutes of daily swimming did not (van Meeteren et al. 1998). The translation of these results to humans with inflammatory PN is also difficult as chemical mediators and processes in inflammatory, immune mediated neuropathy may be different to those after an acute isolated injury to a single nerve root.

A few studies in people with PN have reported that increased muscle activity is detrimental to muscle strength. One cross sectional study of 106 people with CMT attributed reduced strength in the dominant hand (a reversal of findings in healthy people) to over use during activities of daily living, although the data did not demonstrate cause and effect (Vinci et al. 2003). Another report from a heterogeneous group of ten participants, including people with muscular dystrophy and CMT, observed a significant decrease in eccentric peak torque in the elbow flexors after 12 weeks of strength training (Kilmer et al. 1994). Participants increased the frequency of training from three to four days a week and increased repetitions from one set of 10 repetitions to five sets of 10 repetitions. The reduction in eccentric torque of the elbow flexors was attributed to damage produced by over work during resistance training, although this seems unlikely as significant increases in isometric and concentric strength in the same muscle group were evident, and there were significant improvements in the strength of the knee extensors which were trained identically. It is perhaps more likely that this finding was an artefact of the small sample and/or due to deterioration in a small number of participants with muscle disease which skewed results.

In other studies, people with hereditary PN have demonstrated no evidence of overuse weakness after exercise and several have shown significant increases in strength after training at moderate and high intensities (Aitkens et al. 1993; Chetlin et al. 2004; Lindeman et al. 1995). Therefore, it appears unlikely that over work weakness will affect muscle strength after exercise in people with PN. However, the absence of studies in inflammatory PN indicates that

any programme containing strengthening exercises should be monitored for signs of increasing muscle weakness.

Aerobic exercise

Reduced cardiovascular fitness is common in people with neuromuscular disease (Kilmer 2002; Nollet and Beelen 1999). Loss of aerobic fitness is attributed to, but may also exacerbate, reduced physical activity (Rimmer 1999) and is likely to increase the risk of heart disease and other medical problems (Bean et al. 2004). Aerobic training comprises raising heart rate above a percentage (usually 55% or 65%) of maximum heart rate (American College of Sports Medicine 1995). It is recommended that this is maintained for at least 20 minutes, three to five times per week to produce changes in cardiovascular function and endurance which are evident after at least four weeks (Haskell et al. 2007; Pollock et al. 1998). Longer term health benefits associated with improved cardiovascular fitness including lowering the risk of stroke, diabetes and coronary heart disease which become evident with continued training (Bean et al. 2004).

Participation in regular aerobic training has shown widespread benefits in healthy and ageing populations and in people with osteoarthritis, lung and circulatory problems (Bean et al. 2004; Brach et al. 2004). Studies in MS and after stroke have shown significantly increased exercise capacity, fitness and ADL after aerobic training (Petajan et al. 1996; Rietberg et al. 2005; Saunders et al. 2009). In a systematic review by Voet et al. (2009), aerobic training was concluded to be not harmful and possibly of benefit for people with muscle diseases although this was based on only one controlled, unblinded study of 20 participants that met the inclusion criteria.

In a small study of seven people with post polio syndrome, the energy used when walking was significantly improved after six weeks of 30 minutes, thrice weekly aerobic treadmill training at 55%-70% of age predicted maximal heart rate when compared to non-exercising controls, although this occurred in the absence of significant changes in aerobic fitness (Dean and Ross 1991). One other uncontrolled study reported improved resting heart rates after 12 weeks of walking for 15 to 30 minutes three to four times per week at 50-60% of age predicted maximal heart rate in eight people with muscular dystrophy or CMT (n=3) (Wright et al. 1996). They concluded that participants had improved their cardiovascular fitness although changes in peak power and oxygen consumption were not significantly different when tested on a bicycle ergometer. However, the differences in testing and training modalities, the small number of participants and the absence of a non-exercising control reduces the strength of the results of both of these studies (Dean and Ross 1991; Wright et al. 1996).

Two studies have examined aerobic training exercise programmes in people with inflammatory PN (Garssen et al. 2004; Pitetti et al. 1993). The first, a single case study, described the effects of aerobic training in a man three years after GBS, who undertook 30 minutes of thrice weekly, aerobic bicycle training at an intensity of 75-80% of his peak exercising heart rate (Pitetti et al. 1993). After 16 weeks, he demonstrated increased aerobic capacity, increased

peak workload and decreased resting heart rate during exercise testing on a cycle ergometer. The participant also reported reduced experienced fatigue and increased ability in activities of daily living but these were not assessed formally. Whilst these results imply improved cardiovascular fitness, their validity is limited due to the single case, unblinded and uncontrolled design.

A second study examined changes in health related quality of life, experienced fatigue, participation and wider measures of health in people with inflammatory PN after aerobic training (Garssen et al. 2004). Twenty participants at least 12 months after GBS or with stable CIDP exercised for up to an hour thrice weekly in a hospital setting using a cycle ergometer, whilst medically supervised. Although two participants did not complete the programme (one was diagnosed with cardiovascular disease and one did not adhere to the programme), significant improvements in peak power output, oxygen consumption and peak heart rate were found after 12 weeks of training. Reported fatigue was also significantly improved, as were reports of physical functioning, mood and participation. Two years after completion of the programme, peak power, mood and experienced fatigue remained significantly improved from baseline (Garssen et al. 2005a). Ten participants (50%) reported continuing exercise, suggesting they perceived it to be beneficial, but their report was likely to be biased by a desire to please the rater and it is unclear why others chose not to continue exercising. Whilst promising, the strength of these results was limited by lack of blinding, the absence of a non-exercising PN control group and biased by the expectations of participants and investigators. However, the reported changes indicate that aerobic exercise could be beneficial in people with inflammatory PN. They also show that wider measures of health which are associated with persistent activity limitations in this patient group, including fatigue, were improved after an intervention of this nature (Merkies et al. 1999).

Although these findings provide some support for the inclusion of aerobic training in future exercise programmes in people with PN, greater benefits might have been apparent if strength training had been included in addition to aerobic exercise. This combined type of programme, discussed below, is more similar to that prescribed in clinical practice and to programmes recommended by exercise authorities (American College of Sports Medicine 1995).

Combined training

Benefits from both strength and cardiovascular exercise can be produced by an exercise programme which combines both types of training and it is unlikely that this combination would significantly lessen the benefits of each component (McCarthy et al. 1994). Indeed, strength training could actually improve the ability to train aerobically, by increasing the strength of muscles used during aerobic exercise and so have a superior effect than one modality alone (Brill et al. 2000; Clark et al. 1996; Panton et al. 2004).

A combination of strength and aerobic training produced significant improvements in strength, gait speed, activity, the ability to climb stairs and reported functioning in a RCT of six months of exercise in 96 people with MS (Romberg et al. 2004). In addition to strength and aerobic

training, combined programmes often include exercises targeted at specific functional difficulties experienced by the individual. Inclusion of such exercises, for example to improve balance and functional activities (e.g. rising from a chair), have been significantly associated with improved timed performances and reduced activity limitations in two uncontrolled prospective studies in 45 people after stroke (Eng et al. 2003; Leroux 2005).

In their prospective controlled study, Ruhland (1997) included general exercises in addition to aerobic and strength training, but these were not targeted to improve specific functional problems (Ruhland 1997). Fourteen participants with CIDP, CIAP and hereditary neuropathies trained daily in their local community for six weeks, performing a combination of aerobic and strengthening exercise with general exercises (prone scapular retraction, back extension and abdominal curls) (Ruhland 1997). The exercise protocol comprised resisted upper limb exercises (using resistive band) and walking for 10 to 20 minutes at 60% to 70% of age predicted maximal heart rate. A control group (n=14) completed all outcome measurements but did not undertake exercise. One participant fell during training, but other practical issues related to community based exercise and adherence were not reported. After training, participants increased their average muscle score from baseline, becoming significantly stronger than non-exercising controls. Forced vital capacity (FVC), a measure of lung function, was not significantly changed from baseline. Although the authors concluded that this indicated that the participants' cardiovascular fitness was unchanged after training, FVC is unlikely to be a sensitive measure of aerobic function. Significant changes in strength did not appear to be carried over to daily function and performance as only small improvements were reported which were similar to controls. The reason for this is unclear but larger changes may have been seen if the training had continued for longer, as some participants required several sessions before they could exercise at recommended intensities. Continuance of exercise beyond the intervention period was also not measured despite maintenance of health behaviours being necessary to promote long term health benefits (Dishman 1990). The limitations of this study include lack of assessor blinding and incomplete randomisation (as eight from 28 participants were not randomly assigned to control or training group). In addition, the relatively small sample, short training period, absence of follow up beyond the exercise intervention and lack of detail about the practicality of the community based programme reduce the usefulness of these findings.

Whilst the evidence is limited, combined strength, aerobic and functional training is likely to be the most appropriate programme for people with PN. A programme of this nature, which is unsupervised and based in the community, could be maximally beneficial to facilitate regular exercise to reduce persistent disablement in people with inflammatory PN. A possible disadvantage of a combined programme is that it requires participants to undertake several different forms of exercise correctly and effectively, which may make it difficult or necessitate close supervision that is not available in the community. It is also unclear if participants would be willing to exercise regularly and independently. Therefore, the practicality and acceptability

of this type of intervention requires evaluation. This is the first aim of this thesis and is reported in Chapter Two.

1.10. Experienced and physiological fatigue in people with peripheral neuropathies

The second aim of this thesis was to investigate and describe the nature of fatigue in people with PN. In a series of 113 people after GBS, with CIDP or PDN, severe feelings of fatigue were reported by 80% (Merkies et al. 1999). These feelings of fatigue were significantly associated with poorer perceived health and functioning in people with PN but were not predicted by disease severity and little is known about factors that may contribute to them (Garssen et al. 2004; Merkies et al. 1999).

1.10.1. Operational definitions of fatigue

The meaning of the term fatigue is ambiguous. It is often used to describe feelings of tiredness, lassitude and lack of energy (Krupp and Pollina 1996). It can also represent physiological and chemical changes within the neuromuscular system, which result in a reduction in muscle performance (Gandevia 2001).

For clarity different types of fatigue have been defined, producing three operational definitions which will be used throughout this thesis. These are:

Experienced fatigue: “Feelings of fatigue, tiredness, lassitude and/or lack of energy” (Krupp and Pollina 1996; Piper et al. 1989).

Physiological fatigue: “A reduction in the ability of a muscle to produce or maintain force due to changes within the neuromuscular system” (Gandevia, 2001).

Some experienced fatigue is likely to be normal, therefore abnormal, severe experienced fatigue is also defined :

Severe experienced fatigue: “An excessive, abnormal feeling of tiredness or lack of energy which is not relieved by rest” (Krupp and Pollina 1996; Piper et al. 1989).

Few studies have investigated potential causes of severe experienced fatigue in people with PN. One cross sectional study reported reduced neuromuscular endurance¹ in 29 people with hereditary PN, compared to healthy participants, during a sustained contraction of the knee extensors. A smaller study of 15 people with neurogenic weakness (including some PN) also found reduced neuromuscular endurance when the force decline during sustained contractions of the knee extensors and ankle dorsiflexors were compared to healthy controls (Lindeman et al. 1999; Milner-Brown and Miller 1989). Conversely, others found significantly greater muscular endurance in people with diabetic PN (n=44) and after GBS (n=40) when compared to healthy controls (Andersen 1998; Dornonville de la Cour and Jakobsen 2005). However, these studies tested force during repeated isokinetic contractions, rather than the sustained contractions used by Lindeman et al. (1999) and Milner Brown (1989), which could account for

¹ Neuromuscular endurance was defined as the ability of the neuromuscular system to continue to work at a given intensity (Gandevia 2001). This is examined by measuring changes in the force output of the muscles under test.

the different findings of these studies. In addition, several of these studies included participants with metabolic or hereditary PN or a range of neuromuscular conditions, which means their findings cannot be directly transferred to inflammatory PN.

Three studies have investigated the association between other factors, physiological and experienced fatigue in people with inflammatory PN. These are discussed in greater depth in Chapters Five and Six. In brief, Merkies et al. (1999) found that general strength, sensation, age and duration of symptoms were not significantly associated with experienced fatigue in 113 people with inflammatory PN. Similar results were reported by Garssen et al. (2006) in 100 people after GBS, although they found that more severe experienced fatigue was significantly associated with an age over 50 years and being female (Garssen et al. 2006c) . In a smaller study of 10 people several years after GBS, they also reported no associations between changes in the physiological muscular fatigue of the biceps brachii, nerve conduction velocity, functional limitations at nadir and experienced fatigue (Garssen et al. 2006a) .

The absence of significant associations in these studies suggests that other factors which were not measured could contribute to more severe experienced fatigue. These factors, such as the physiological fatigue of functional, weight bearing muscles and cardiovascular fitness, should be investigated to aid understanding and develop targeted treatments.

Although treatments to reduce experienced fatigue in people with PN appear elusive (Garssen et al. 2006), experienced fatigue has been significantly reduced after exercise interventions (Garssen et al. 2004; Garssen et al. 2005a; Pitetti et al. 1993). Whilst this suggests that exercise has a potential role in reducing fatigue, it also indicates that the factors improved by exercise may contribute to the severity of experienced fatigue.

If possible contributors to experienced fatigue could be identified, targeted treatments could be developed to reduce its severity and reduce the activity limitations associated with it. This investigation is presented in Chapters Five and Six.

1.11. Review of outcome tools

1.11.1. Background

Outcome tools for the exercise study (Chapter Two) were pre-selected by a project steering group (Appendix One).

In this section, although pre-selected, these tools are described and critically evaluated to allow the results they provide to be viewed in light of their properties. Tools that were used in other studies in this thesis are also critically considered.

Where possible tools were appraised under the standard headings of impairments in body structure, activity limitations and participation restrictions (Salter et al. 2005b; Salter et al. 2005a; Salter et al. 2005c; World Health Organisation 2001). However, whilst categorised under one International Classification of Functioning (ICF) descriptor, it is acknowledged that many tools assess more than one aspect of functioning and some contain items that are not explicitly included in ICF (Salter et al. 2005b; World Health Organisation 2001).

1.11.2. Considerations when appraising an outcome tool

Perhaps the most important and obvious consideration when appraising an outcome tool is that it provides the information that is wanted. Other important factors include its reliability, validity, floor and ceiling effects and responsiveness to ensure that the changes on the outcome tool are not caused by random error, that the tool measures what it purports to, and that it is sufficiently sensitive to reflect alterations in status (Lohr et al. 1996; Wade 1992b). Consideration of practical issues, for example the time taken to complete and the simplicity of the scale (burden), the acceptability to the patient, the usefulness, the interpretability and ease of communication of the information yielded by the tool, the ability to detect the predominant issues of the patient group of interest, and the clinical meaning of scores are also important. Consideration of these factors indicate if a tool is appropriate (suited to its application) and suitable (adapted for the characteristics of the patient group) (McHorney 1998; Wade 1992b). The recommendations of specialist bodies also informed the appraisal of the pre-selected outcome tools. The European Neuromuscular Centre group guidelines were used; this group comprises 23 international representatives including neurologists, neurophysiologists, pharmaceutical scientists with interests in PN, and a patient representative of the Guillain-Barré Syndrome Foundation International (Merkies and Lauria 2006). The conclusions of the British Society of Rehabilitation Medicine were also used (British Society of Rehabilitation Medicine 2000). These recommendations were used cautiously alongside considerations discussed above in appraising each tool as it was recognised that they are likely to be influenced by personal opinion and bias.

1.11.3. Considerations specific to people with PN

As discussed in Sections 1.6, 1.7 and 1.8, common impairments in PN include altered sensation, experienced fatigue, altered mood and muscle weakness (Forsberg et al. 2004; Gorson et al. 1997; Hughes and Cornblath 2005). Activities such as walking and completing daily tasks are often affected (Erdmann et al. 2005; Forsberg et al. 2005; Gorson et al. 1997;

Lunn et al. 1999) and significant participation restrictions which necessitate changing jobs and/or hobbies are experienced by some (Bernsen et al. 2002; Bersano et al. 2005). The inclusion of these problems in an outcome tool adds to its suitability for people with PN and was considered when evaluating the selected tools.

1.11.4. Limitations of outcome tools

The majority of outcome tools share some limitations which are inherent to the type of data they generate. Whilst specific limitations are considered in context of each tool, to avoid repetition generic limitations are considered here.

A common inadequacy of the data yielded by many outcome tools is that it is based solely upon participant report which can be biased or inaccurate (Rubenstein et al. 1984). The accuracy of self report is affected by a range of factors including gender, motivation, desire to please the rater and mental health (Goverover et al. 2005; Kempen et al. 1996; Rubenstein et al. 1984). A response shift, when respondents recalibrate their perception of their health often due to changes in health, influences self report and typically results in an underestimation of change by respondents (Schwartz et al. 2006; Schwartz and Spranger 1999). Although observation or proxy report might improve on some of the limitations of self report, they are still affected by bias and some constructs are impractical or impossible to measure by observation or from proxy report, for example experienced fatigue or the participant's perception of their health (Ottenbacher et al. 1996).

A further limitation is that many tools do not provide any information about why the participant is unable to complete activities or participate in life situations and cannot indicate the importance placed upon the activity by the individual. Although qualitative methods could provide these data, they do not facilitate direct comparison before or after intervention (Chapter Two) or between groups (Chapters Five and Six) and so were not appropriate for studies in this thesis. Finally, it is important to recognise that the properties of outcome tools are based upon the findings of others in published work which may be unavoidably biased by the opinions of the authors and publication bias (Cleophas and Cleophas 1999). Although these limitations are inherent to most published outcome tools, they are important to take into account when drawing conclusions from the data they yield.

1.12. Body structure and function

1.12.1. Muscle strength

Muscle strength is a commonly used indicator of motor impairments in people with inflammatory PN (Merkies and Lauria 2006; Trigg and Wood 2003). Isometric muscle strength was measured using fixed dynamometry in the knee extensors in Chapter Two and by an isokinetic Kin Com dynamometer set in the isometric mode in the knee extensors in Chapter Six. Strength of muscles was graded in studies in Chapters Three and Four using the Medical Research Council (MRC) sum score (Medical Research Council 1976). A limitation of all these voluntary strength measures is that they assume that participants are making maximal effort. Submaximal efforts can be mistaken for weakness but this can be minimised by providing standardised verbal encouragement and adequate familiarisation (McNair et al. 1996).

This chapter discusses the properties of fixed dynamometry (used in Chapter Two) and the MRC sum score measurements (used in Chapters Three and Four); the Kin Com dynamometer is considered separately in Chapter Six.

Fixed dynamometry

Measurement using fixed dynamometry is considered to be the criterion standard of strength measurement (Aitkens et al. 1989). In Chapter Two, peak isometric knee extension force was measured using a fixed strain gauge. Lever arm length (between the centre of the knee joint and ankle cuff) was not incorporated in force calculation, therefore linear force was expressed in Newtons (N). The equipment used to measure knee extensor strength in these studies was reliable at forces up to 196 N as 20 repeated measurements, taken over three months using known weights up to 20 Kg were accurate and closely associated ($r=0.99$) (Appendix Two). However, it was not possible to assess reliability at higher forces.

Medical Research Council Sum Score

The strength of muscles was graded using the Medical Research Council (MRC) sum score (Medical Research Council 1976). It was first used to grade strength after peripheral nerve injuries, and is now used in neurological practice around the world, being used in over 13 published studies in inflammatory PN (Dyck et al. 2005). It is considered a valid measure of muscle strength in neuromuscular disease and is quick and easy to administer (Aitkens et al. 1989). A MRC score ranging from zero (muscle paralysis) to five (normal strength) is assigned by the examiner who grades strength by resisting a maximal isometric contraction of the muscle group under test.

The total sum score is calculated by summing the grades for the following muscle pairs, to give a total from 60: shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors and ankle dorsiflexors which are tested in standardised positions (Kleyweg et al. 1991; Medical Research Council 1976).

The MRC sum score demonstrated good test re-test reliability when used in 102 people with neuromuscular disease (Florence et al. 1992), high overall inter-rater reliability (ICC= 0.96)

and was sensitive to change in clinical status in 113 people with GBS (Kleyweg et al. 1991; Merkies et al. 2003a). However, it may be insensitive to strength changes in muscles which display between 25% and 75% of full strength (Aitkens et al. 1989; Dyck et al. 2005). The relationship between MRC grades and fixed dynamometry has also not been established in neuromuscular disease and as MRC sum score grades are not linear, they are unlikely to be equivalent to dynamometry measurements which challenges the validity of the MRC sum score (Dyck et al. 2005). For these reasons, the MRC sum score was only used to indicate the strength of people with PN and was not used to judge change after an intervention. As the reliability of MRC scores was likely to be influenced by rater training and experience (Kleyweg et al. 1991) a single rater who was well practiced in using the sum score was used if consecutive measurements on the same patient were required. Standardised testing positions were also used to increase reliability (Kleyweg et al. 1991; Medical Research Council 1976).

1.13. Impairments

1.13.1. Experienced fatigue

There is no single criterion fatigue scale and at least 30 self report tools to measure experienced fatigue have been identified (Dittner et al. 2004; Friedberg and Jason 1998). Tools were not considered for use in the studies in this thesis if they only indicated a specific feature of fatigue e.g. cognitive fatigue, or if they could not describe the aspects of functioning most affected by fatigue e.g. a single visual analogue scale of fatigue severity. Tools that contained several items which reflected physical problems of fatigue, such as muscle weakness, were also excluded as they could erroneously attribute common physical impairments experienced by many people with PN to symptoms of more severe fatigue, confounding results. Respondent burden particularly influenced selection as long questionnaires are thought to further exacerbate symptoms in those who have fatigue, especially when part of a battery of other assessments (Dittner et al. 2004; Merkies et al. 1999).

The Fatigue Severity Scale (FSS) was pre-selected as the sole tool to measure fatigue in the study of exercise in Chapter Two. Two additional tools, which were also designed to reflect experienced fatigue, were also used in the investigation of fatigue in Chapters Five and Six: the fatigue impact scale and the revised Piper fatigue scale. A brief description of each of the three scales is provided and followed by a review of their advantages and limitations.

The fatigue severity scale

The fatigue severity scale (FSS) is a unidimensional questionnaire and has nine items which measure the behavioural consequences and symptoms of fatigue (Krupp et al. 1989; Taylor et al. 2000). Each item on the FSS is answered by selecting one response from a seven point scale; a higher score indicates more severe fatigue. The overall score is found by calculating the mean of the scores from each item.

The fatigue impact scale

The fatigue impact scale (FIS) is a multi dimensional questionnaire which reflects the reported impact of fatigue upon a range of activities (Fisk et al. 1994). It allows delineation of the effects of fatigue in three areas: physical (ten items), cognitive (ten items) and psychosocial function (20 items). Each item is scored on a five point (0-4) Likert scale, to reflect how much difficulty this aspect of fatigue has caused in the last month. A higher score indicates greater fatigue. Subsection and total FIS scores are calculated by summing each item (total FIS score: 160).

The revised Piper Fatigue Scale

The revised Piper Fatigue Scale (PFS) is a multidimensional questionnaire which assesses the perceived intensity of fatigue (Piper et al. 1998). Respondents are asked to rate the severity of specific aspects of their fatigue out of ten on 22 items; a higher score indicates greater experienced fatigue (Piper et al. 1998). In addition to a total score, dimension scores from behavioural severity (six items), affective meaning (five items), sensory (five items) and cognitive affect and mood (six items) are calculated. A score is generated by adding the numerical answers given in each dimension, and then dividing by the total number of items answered. A score of ten indicates most severe fatigue. Scores less than seven are reported to indicate moderate fatigue and below three, mild fatigue (Piper et al. 1998).

1.13.2. Evaluation of outcome tools measuring experienced fatigue

Advantages

These tools have been used widely in other conditions, but only the reliability and validity of the FSS has been evaluated in PN. Merkies et al. (1999) reported significant differences in FSS scores between 113 people with inflammatory PN and healthy participants, indicating divergent validity and the concurrent validity of the FSS was supported as scores in the PN group were significantly associated with energy and vitality scores on the SF-36 questionnaire (Merkies et al. 1999). The FSS scores were also internally consistent (Cronbach's $\alpha = 0.93$) and repeated measurements over several months were strongly associated ($r = 0.86$), inferring it was reliable (Merkies et al. 1999). In comparison to the other reviewed fatigue outcome tools, the FSS has the fewest items, and so has low respondent burden; it is also reported to have a high level of correct completion (95%, 57 from 60 participants with MS) (Chipchase et al. 2003; Friedberg and Jason 1998). These findings suggest that the FSS is suitable for people with PN and could yield important information about experienced fatigue in the studies in this thesis without adding considerably to respondent burden.

The FIS, unlike the FSS, is a multidimensional fatigue scale and so could provide greater insight into the effect of experienced fatigue upon distinct aspects of functioning. It has demonstrated a relatively high correct completion rate in people with MS (88%) (Fisk et al. 1994) but it contains 40 items and so has a greater burden than the FSS. The FIS has been used to measure perceived experienced fatigue in several conditions including chronic fatigue syndrome (CFS) and MS but has not been evaluated in PN (Fisk et al. 1994; Paul et al. 2000).

It has demonstrated internal consistency (Cronbach's $\alpha > 0.8$) and discriminated between 145 people with MS, 105 people with CFS and 34 people with heart disease, demonstrating divergent validity (Fisk et al. 1994; Paul et al. 2000). It has also shown responsiveness to changes in fatigue after targeted drug treatment in 218 people with MS (Metz et al. 2004), although an estimate of its responsiveness was not given and responsiveness in PN cannot be assumed. Although the reliability, validity and responsiveness of the FIS have not been evaluated in people with PN, it has been used to capture change, showing a 20% decrease in fatigue in 20 participants with PN after a 12 week supervised exercise intervention (Garssen et al. 2004). Its significant burden and the lack of evidence evaluating its properties in PN deter from using the FIS as a single indicator of fatigue or if detailed assessment of fatigue is not warranted. However, the performance of the FIS in other patient groups and its ability to reflect distinct aspects of fatigue supports its use alongside other tools to describe experienced fatigue in the investigations of fatigue in Chapters Five and Six.

The PFS has not been used as widely as the FSS and FIS in neurological conditions and has not previously been used in PN. The PFS has a greater burden than the FSS as it has 22 items but, unlike the FIS and FSS, it yields information regarding the intensity of experienced fatigue. Its properties have been investigated in 64 people with post polio syndrome (Strohschein et al. 2003). A strong association with scores on another fatigue scale, the Modified fatigue inventory ($r=0.8$) supported its validity, it also had face and content validity, excellent internal consistency (Cronbach's $\alpha = 0.98$) and high test re-test reliability over short periods (ICC=0.98) in this patient group (Strohschein et al. 2003).

The PFS was selected to be used alongside tools which indicate functional and affective components of experienced fatigue to provide information about the intensity of experienced fatigue in the investigations of fatigue in Chapters Five and Six.

Disadvantages

All experienced fatigue outcome tools reviewed here have some similar disadvantages. In addition to the limitations of self report (discussed on Page 44), these questionnaires assume that fatigue reported by participants is similar to normal fatigue experienced by most people, but is of greater intensity or severity and consequently produces limitations (Taylor et al. 2000). However, people with severe experienced fatigue could undergo a qualitatively very different and individual experience of fatigue, which would not be captured comprehensively by standardised outcome tools. Although qualitative investigation of the perception of fatigue overcomes this limitation, it would not allow comparison between groups or before and after an intervention in the same group, so would be inappropriate for the studies in this thesis.

Whilst the FSS has been positively evaluated in people with PN, it has several limitations. Respondents completing the FSS may score highly on one specific item ("my motivation is lower when I am fatigued"), in the absence of experienced fatigue, as it could be argued that most people experience reduced motivation when fatigued. Similarly, some items on the PFS are also dependent upon the respondent's perception of their fatigue, (e.g. "the fatigue I am

experiencing is pleasant or unpleasant”), rather than simple fatigue intensity. This could be overcome by comparing results from the FSS and PFS to those from healthy respondents to determine if totals could be judged to be abnormal. The validity of the PFS may be reduced if respondents have difficulty completing a numerical rating scale; this has been reported on other tools which use similar scales (Friedberg and Jason 1998; Strohschein et al. 2003). A ceiling effect on the PFS has also been reported in healthy participants which indicates it has decreased sensitivity to milder experienced fatigue which should be considered when reviewing the results in Chapter Five (Strohschein et al. 2003).

1.13.3. Mood

The mood, mental health or well-being of people with PN has not been widely evaluated, possibly because it is not directly affected by the neuropathic process. However, low mood can be caused by, and contribute to, persistent activity limitations and reduced quality of life in people with PN, and thus warrants measurement (Bernsen et al. 2002; Lennon et al. 1993). The HADS and BDI were used to measure anxiety and depression in Chapter Two. Each tool is described separately and their advantages and disadvantages considered together.

Hospital anxiety and depression scale

The hospital anxiety and depression scale (HADS) is a self completed 14 item questionnaire, which takes less than five minutes to answer (Snaith and Zigmond 1994). It measures generalised anxiety and loss of pleasure response on anxiety and depression subscales (seven items each). The anxiety and depression subscales are scored separately where a score less than seven is considered normal; scores below ten indicate mild levels of anxiety or depression and, below 14, moderate. If participants score above 15, they are considered severely anxious or depressed (Snaith and Zigmond 1994).

Beck depression inventory

The Beck depression inventory (BDI, version 2, BDI-II) is a 21 item questionnaire which measures the severity of depression (Beck et al. 1996). It was developed by refining items from the original Beck scale in 1996 (Beck et al. 1996; Steer et al. 1999). Scores below 13 indicate minimal or no depression, below 19 mild depression and scores over 28 severe depression (Beck et al. 1996).

1.13.4. Evaluation of tools to measure mood

Advantages

The HADS is a valid indicator of both anxiety and depression, and has been used in over 700 reported studies with more than 10,000 participants (Bjelland et al. 2002; Snaith and Zigmond 1994). It has been used in neurology and primary care settings, and in people with and without clinical levels of anxiety and depression (Bjelland et al. 2002; Snaith and Zigmond 1994). The BDI has also been used extremely widely in mental health and community settings (Beck et al. 1996; Steer et al. 1999).

The HADS has been shown to be internally consistent (Cronbach's $\alpha > 0.6$) (Bjelland et al. 2002) and reliable over at least six weeks (correlation between repeated scores exceeded 0.7) when re-tested in 900 people with and without clinical levels of anxiety and depression (Herrmann 1997). Similarly, the BDI is also reported to be internally consistent (Cronbach's $\alpha = 0.9$) and its test re-test reliability excellent in a range of patient groups (overall $r = 0.93$) (Ambrosini et al. 1991; Beck et al. 1996).

The HADS (depression scale) and BDI correlate significantly with each other suggesting they are valid (Bjelland et al. 2002). The HADS has also demonstrated significant associations with other measures of mood in healthy volunteers and psychiatric patients including visual analogue scales ($r > 0.6$) (Bjelland et al. 2002).

In a review of 24 studies, the cut off value on the HADS after which anxiety and depression are considered abnormal was similar to that identified by its authors (>7) indicating it is able to detect low mood (Bjelland et al. 2002). Similarly, the cut off point of 13 on the BDI detected abnormal levels of depression with sensitivity of over 80% in 122 younger people in primary care (Ambrosini et al. 1991). The responsiveness of the BDI and HADS after exercise interventions has not been formally reported. However, the HADS was used to measure change after an exercise intervention in 20 people with PN, demonstrating significant changes (Garssen et al. 2004). The BDI also measured significant changes in depression after an exercise intervention in people with clinical depression, but it is not known if it would behave similarly in people with PN who are not clinically depressed (Lawlor and Hopker 2001).

Disadvantages

The BDI and HADS have some drawbacks which should be considered when viewing the data they produce. Neither have been fully evaluated in PN and although both have been used in studies of exercise, it is unclear how responsive they would be to changes after an exercise intervention in people whose scores indicate normal levels of anxiety and depression (scores below seven and 13 on the HADS and BDI respectively). The validity of BDI scores is reduced in people with lower scores (Ambrosini et al. 1991) which implies its validity cannot be assumed in people with PN without depression. The BDI may also not be able to distinguish symptoms of depression from anxiety, reducing its validity to reflect depression alone (Richter et al. 1998).

Although the HADS was developed to describe mental health in people with physical problems, some items describe physical symptoms which reduces its face validity e.g. "I feel as if I am slowed down...". Similarly on the BDI, items indicate other impairments experienced by people with PN (e.g. fatigue), which would be erroneously be attributed to depression. This would artificially inflate scores. Furthermore, the cut off values after which anxiety and depression are considered abnormal on the HADS may be inaccurate for people with reduced functioning, as lower values were found in people after stroke (scores greater than five indicated anxiety, and greater than four indicated depression) (Bjelland et al. 2002). This suggests that normative cut off values should be used with caution in people with PN.

Whilst the HADS detects anxiety and depression, the BDI provides a greater insight into the severity and nature of depression and has been used to evaluate changes in mood after exercise. Both tools were used in the investigation of exercise (Chapter Two) and their performance was re-evaluated after their use.

1.14. Activity limitations

Activity limitations refer to difficulties experienced by an individual when carrying out a task or action (World Health Organisation 2001). Changes at the level of activities are argued to be most important to the individual and so are the most suitable to evaluate rehabilitative interventions (Wade 1999). Therefore, changes in activities were selected to be the primary outcome of the exercise intervention (Chapter Two). This section reviews the properties of tools which measure activity and is subdivided into those which evaluate activities of daily living (ADL), extended activities of daily living (EADL) and specific activities of mobility and walking.

1.14.1. Activities of Daily Living

Activities of daily living (ADL) are stated to be tasks “...which everyone will need to accomplish every day, (or at least every week with some items).” (Wade, 1992d; p71). Activities which constitute activities of daily living are widely agreed to include: mobility, grooming, bathing, feeding and dressing (Dittmar and Gresham 1997).

Overall disability sum score

The Overall disability sum score (ODSS) was designed to measure reported activity limitations in people with inflammatory PN (Merkies et al. 2002a). It was developed from a consensus of experts in order to address the perceived lack of suitable outcome tools in PN and consists of a checklist with five upper and lower limb items, including dressing, grooming and mobility. It is administered as an interview, taking less than two minutes to complete (Merkies et al. 2002a). Raters are instructed to calculate an overall score by summing upper and lower limb scores. A maximum score of 12 indicates inability to use the upper or lower limbs for purposeful movement, zero indicates no limitations.

The ODSS questionnaire is shown overleaf.

The Overall Disability Sum Score (ODSS)

ARM DISABILITY SCALE – Function checklist

	Not affected	Affected but not Prevented	Prevented
Dressing upper part of body excluding buttons or zips	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Washing and brushing hair	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Turning a key in a lock	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Using a knife and fork (/spoon if patients never uses knife or fork)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Doing or undoing buttons or zips	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Arm Grade

0 = Normal

1= Minor symptoms or signs in one or both arms but not affecting any of the functions listed

2= Moderate symptoms or signs in one or both arms affecting but not preventing any of the functions listed

3= Severe symptoms or signs in one or both arms preventing at least one but not all functions listed

4= Severe symptoms or signs in both arms preventing all functions listed but some purposeful movement still possible

5= Severe symptoms or signs in both arms preventing all purposeful movements

SCORE =

LEG DISABILITY SCALE – Function checklist

	No	Yes	Not Applicable
Do you have any problem with your walking?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you use a walking aid?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
How do you usually get around for about 10 metres?			
Without aid	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
With one stick or crutch or holding to someone's arm	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
With two sticks or crutches or one stick or crutch holding onto someone's arm	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
With a wheelchair	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>If you use a wheelchair, can you stand and walk a few steps with help?</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
If you are restricted to bed most of the time are you able to make some purposeful movements?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Leg grade

0= Walking is not affected

1= Walking is affected but does not look abnormal

2= Walks independently but gait looks abnormal

3= Usually uses unilateral support to walk 10 metres (25 feet) (stick, single crutch, one arm)

4= Usually uses bilateral support to walk 10 metres (25 feet) (sticks, crutches, two arms)

5= Usually uses wheelchair to travel 10 metres (25 feet)

6= Restricted to wheelchair, unable to stand and walk few steps with help, but able to make some purposeful leg movements

7= Restricted to wheelchair or bed most of the day, preventing all purposeful movements of the legs (e.g. unable to reposition legs in bed)

SCORE=

Overall disability sum score = arm disability scale (range 0-5) + leg disability scale (range 0-7);

Overall Range: 0 (no signs of disability), 12 (maximum disability).

For the arm scale: allocate one arm grade only by completing the function checklist,

indicate whether each function is "not affected", "affected but not prevented" or "prevented".

For the leg disability scale: Allocate one leg grade only by completing the functional questions

Evaluation of the overall disability sum score

The ODSS has not been widely investigated in PN and so appraisal of its properties is limited and based upon studies by its authors, placing them at particular risk of bias (Merkies et al. 2002a). The association between scores on the ODSS and other established ADL measures has also not been reported which challenges its validity. Despite these limitations, the ODSS has been used in several clinical trials and investigations and has been recommended as an outcome tool in trials in PN (Hagemans et al. 2005; Hughes et al. 2004; Merkies and Lauria 2006; Merkies et al. 2003b; van Doorn and Garssen 2002).

Two studies by the authors of the ODSS have considered the reliability, validity and responsiveness of the ODSS (Merkies et al. 2002a; Merkies and Schmitz 2006). The ODSS was reliable (inter and intra-rater intra class correlation coefficients, ICC, > 0.9) in 113 people with inflammatory PN and it correlated strongly with the GBS disability score ($r>0.74$) inferring validity (Merkies et al. 2002a). In the second study, the ODSS was responsive to change in people with PN, demonstrating significant improvements in a smaller but clinically relevant sample of 20 people recovering from GBS examined longitudinally over one year (standardised response mean, SRM= 1.2 to 1.4) (Merkies et al. 2002a; Merkies et al. 2003a). Indeed, it demonstrated the greatest responsiveness of all clinical measures used in this patient group (including hand grip strength, ten metre walk time, nine hole peg test and sensory sum score) (Merkies et al. 2003a).

The ODSS has some face validity as it reflects difficulties in common ADLs such as washing, dressing and mobility (Merkies et al. 2002a). However, some ADLs are omitted, such as showering/bathing, and there is likely to be overlap between items within the ODSS as an inability to perform one activity (e.g. dress) limits the ability to complete others (e.g. fasten buttons). This overlap is common to other ADL tools and although it reflects the usual limitations experienced by the individual, it inflates scores (Kasner 2006).

A limitation of the ODSS, shared by many other ADL tools, is that many items are scored from only two or three options and so could lack sensitivity to small but important changes in activities. This does not appear to be the case as scores on ODSS have been moderately and significantly associated with patient's perception of change ($r=0.66$) (Merkies and Schmitz 2006). Others have found that a change of one point on the GBS disability scale, which is somewhat similar to the ODSS, was considered to be meaningful in people with PN (Hughes 2002c). These findings suggest that the ODSS has adequate sensitivity but its ability to measure changes after an exercise intervention has not been examined. Therefore, the properties of the ODSS were re-evaluated after its use in the study of exercise in Chapter Two.

1.14.2. Extended Activities of Daily Living

Although more difficult to define, extended activities of daily living (EADL), sometimes called instrumental ADL, include tasks which are completed less often and are not necessarily performed by all people, but are governed by choice and circumstance (Wade 1999). These commonly include actions such as crossing roads, washing crockery, shopping and housework.

The health assessment questionnaire disability index

The health assessment questionnaire (HAQ) was one of the first self report measures of functional ability and limitations (Bruce and Fries 2003; Fries et al. 1982). The HAQ disability index (HAQDI), a subsection of the HAQ, captures information about usual daily activities in the past week from eight categories which question specific EADL (e.g. grooming and reaching) and are scored from four levels of difficulty from zero (no difficulty) to three (unable to perform). The highest scored item determines the overall score for that category. The use of aids or adaptations increases the category score by one for scores less than two. The overall score is calculated as the mean of eight categories, with 25 possible scores (Bruce and Fries 2003). A score of zero indicates little or no perceived limitation, and three indicates perceived maximum limitations, and an inability to perform the activities outlined.

Evaluation of the health assessment questionnaire disability index

The HAQDI was originally designed as a part of a larger tool to measure limitations in people with arthritis. Although the HAQDI has not been used in PN, it is argued to be a generic tool by its authors as the constructs underpinning the items (activity limitations and dysfunction) are common to many other long term conditions (Bruce and Fries 2003).

Items on the HAQDI are considered to be appropriate to indicate activity limitations in neurological conditions (Wade 1992a) and they question activities that are widely recognised to be limited in people with PN, e.g. turning taps, opening jars etc. (Bernsen et al. 2005; Erdmann et al. 2005; Merkies et al. 2000). These are not explicitly captured by many other EADL tools, supporting the inclusion of the HAQDI. It is simple, quick and straightforward to complete and has little burden (Wade 1992a). However, the HAQDI demonstrates a problem common to EADL tools as EADLs, by definition, depend upon personal preferences which vary between individuals. Whilst the HAQDI lacks items regarding specific hobbies and pastimes which reduce this limitation, this does mean that it cannot provide any information on some potentially important aspects of EADL. However, this limitation can be overcome if other tools that provide these data were used alongside the HAQDI.

The HAQDI has demonstrated validity in people with a range of orthopaedic problems as its scores have correlated strongly with self reported physical functioning ($r=0.7$, measured on the Medical Outcomes Short Form 36 item questionnaire, SF-36) (Bruce and Fries 2003). However, its validity in PN has not been investigated. Scores on the HAQDI are reported to be consistent and reliable over time in a range of orthopaedic conditions (mean $r=0.98$ over six months) (Bruce and Fries 2003; Fries et al. 1982; Green et al. 2001) and the HAQ has demonstrated moderate responsiveness to changes in 105 people with rheumatoid arthritis over 15 months (Fitzpatrick et al. 1989). Others demonstrated that the HAQDI had good to excellent responsiveness (effect size range : 0.7 - 0.9) in 196 participants with systemic sclerosis who participated in a trial of a new drug (Khanna et al. 2005). These results indicate that the HAQDI is responsive in conditions which produce physical limitations beyond those it was originally designed for. Whilst this adds support to its inclusion, a similar performance in people with PN cannot be assumed.

Furthermore, some items on the HAQDI question ADLs (such as dressing, rising, eating and hygiene) leading to replication of information provided by other tools and potential item redundancy. An additional limitation of the HAQDI is that the scoring criteria lacks some sensitivity, as participants are considered more limited if they use an aid, even though they could depend on the aid considerably less than on previous testing. This difference, although small, could be clinically significant for some respondents but is not able to be reflected by the HAQDI. This may reduce its responsiveness. As the HAQDI has not been used or evaluated in PN previously, its performance was re-examined after its use in Chapter Two.

1.15. Specific components of ADL

1.15.1. Mobility

Mobility comprises a number of ways of moving, including changing and maintenance of body position, walking long and short distances on different surfaces, moving around with and without equipment and moving effectively in normal surroundings (World Health Organisation 2001). Mobility is considered by many to be a key daily function (Chiou and Burnett 1985) and is affected in 7% (of 42) to 26% (of 40) of people at least two years after GBS (Dornonville de la Cour and Jakobsen 2005; Forsberg et al. 2004). In one study of people with chronic inflammatory PN, 80% (of 24) reported difficulty walking and climbing stairs (Erdmann et al. 2005).

As participants included in the studies in this thesis were required to be ambulant for at least part of the day (except for participants in the investigation of the Overall Neuropathy Limitations Scale in Chapter Three), only tools measuring ambulant ability were appropriate. Video and motion analysis, which measures kinematic and kinetic parameters of gait, were not considered for use in this thesis as studies did not specifically target gait, these data do not necessarily reflect usual functioning in the community and have limited clinical relevance (Pearson et al. 2004).

Several of the tools already considered in this chapter measure self reported mobility, notably the ODSS and HAQDI. Therefore, no extra mobility questionnaires were selected to measure mobility in the study of exercise in Chapter Two. However, timed walking tests were used alongside these tools in Chapter Two to provide objective data on parameters of gait.

Three tools, the physiological cost index (PCI) (MacGregor 1979), modified PCI (mPCI) and Walk-12 (Hobart et al. 2003) which measure aspects of walking and mobility were evaluated and developed in Chapter Four, and so are not described here.

Ten metre walk test

Timed tests are one of the most common tools used to indicate mobility (Dittmar and Gresham 1997). In the ten metre walk test participants walk in a straight line along a level surface at their preferred walking pace (preferred pace ten metre walk test) or as fast (fast ten metre walk test) as safely possible whilst being timed. The time taken at a preferred pace is strongly associated with cadence, stride length, balance, reported mobility, lower limb strength and has

discriminated between the use of aids in a range of patient groups including people after stroke and the elderly (Bohannon 1997a; Bohannon and Andrews 1990; Rossier and Wade 2001; Wolfson et al. 1990). The preferred pace ten metre walk test also demonstrated excellent test re-test reliability when measured twice, one week apart (ICC= 0.93) in one study of 46 people with a range of neurological conditions (Rossier and Wade 2001).

The preferred pace ten metre walk test has been used in several studies to describe functioning in people with inflammatory PN (Erdmann et al. 2005; Forsberg et al. 2004) and it has been recommended as an outcome tool in clinical trials in PN by expert consensus (Merkies and Lauria 2006). However, only one study has examined the validity of the ten metre walk test in people with PN. In a small study of 11 people with CIDP, ten metre walk test times had a strong correlation with balance scores ($r=0.76$) and moderate associations with self reported motor functioning ($r= 0.55$) (Erdmann et al. 2005). Whilst this suggests that the ten metre walk test is valid for PN, the small sample considerably limits the strength of this conclusion.

Both fast and preferred pace ten metre walks appear highly responsive to changes in clinical status in other neurological conditions (standardised response mean, SRM= 0.92 and 0.83 respectively) (Salbach et al. 2001). However, one study of 20 people after GBS ($n=7$) or with CIDP ($n=13$) demonstrated that the preferred pace ten metre walking time was poorly responsive to clinical changes which occurred over 12 months (SRM=0.38) (Merkies et al. 2003a). This could be caused by a ceiling effect on the preferred pace test which has been reported by others (Wade 1992c) and implies the test is not responsive for more able participants. However, this ceiling effect could be reduced if participants walk as fast as possible (fast ten metre walk), although this has not been investigated.

A disadvantage of both versions of the ten metre walk tests is that they cannot provide any information about other aspects of mobility that occur in the community such as walking on uneven surfaces or climbing steps. Consequently, despite correlating with cadence and other parameters of gait, they reveal little about the quality and efficiency of usual walking (Bohannon 1997a; Rossier and Wade 2001). However, these areas of functioning are measured by other ADL and EADL tools which have been pre-selected for the study of exercise in Chapter Two. Therefore, both preferred pace and fast ten metre walk tests were selected for use in studies in this thesis.

1.16. Participation

Participation is defined as an individual's involvement in a life situation or role (World Health Organisation 2001) and includes performance of hobbies, employment and fulfilment of family responsibilities. Participation restrictions are therefore influenced by personal and environmental factors. The absence of in depth studies of participation in PN makes it unclear which aspects are the most pertinent and so which participation tools are the most appropriate. The tools used in this thesis are each described separately and then critically considered together.

1.16.1. The Medical Outcomes Survey Short-Form 36 item questionnaire

The Short Form 36 item questionnaire (SF-36) is a simple self administered questionnaire, developed from the Medical Outcomes Survey in North America (Ware and Sherbourne 1992). It is considered to measure aspects of health related participation, health related quality of life or general health status (Merkies et al. 2002c; Salter et al. 2005c; Schepers et al. 2007). The SF-36 (UK, version 1) comprises eight health related subscales including: physical functioning (10 items), role limitations due to emotional (three items) and physical (four items) problems, energy and vitality (four items), pain (two items), mental health (five items), social functioning (two items) and general health (five items) and takes less than ten minutes to complete (Ware and Sherbourne 1992). Answers are transformed, using a scoring algorithm, to produce raw scores from zero (poor health status) to 100 (good health status) for each subscale (Ware and Sherbourne 1992). A ninth scale, health transition, asks participants to rate their health in comparison to one year ago. All other scales require respondents to base their answer upon current health or over the previous month. This SF-36 is most commonly administered as a self completed questionnaire, but can also be completed by an interviewer, over the telephone, via post or by proxy (Salter et al. 2005c).

Raw scores can be summarised in two categories; the physical (PCS) and mental (MCS) component summary scores (Ware and Kosinski 2003) which are interpreted in relation to “norm” based scoring derived from the general population in 1998 so that the score would equal 50 in a healthy population (Ware and Kosinski 2003). A score below 50 indicates poorer health related status, a score greater than 50 indicates better than normal status (Ware and Kosinski 2003).

1.16.2. The functional limitations profile

The functional limitations profile (FLP) (Patrick and Peach 1989) measures the respondent's perception of health related functioning. It consists of 136 weighted items which are summed into an overall percentage score, ranging from zero (no limitations) to 100% (maximum limitation). It is considered to be a participation tool, although some items consider other activities such as eating and drinking (Salter et al. 2005c; Schepers et al. 2007). The FLP is administered as an interview questionnaire and takes up to 30 minutes to complete (Damiano et al. 1999). It contains 12 subscales: ambulation, mobility, body care and movement, household management, recreation and pastimes, social interaction, alertness, emotion, sleep and rest, eating, communication and work. In addition to an overall score, physical and psychosocial subscales are also calculated.

1.16.3. Rotterdam handicap scale

The Rotterdam handicap scale (RHS) was designed to measure restrictions to participation reported by people with inflammatory PN (Merkies et al. 2002b). It was initially developed by a group of neurologists and items were refined following interviews with 12 PN patients and a paper survey of 38 PN patients (Merkies et al. 2002b). It comprises nine items with five possible answers and takes less than four minutes to complete (Merkies et al. 2002b). The

items investigate transport and occupation, indoor and outdoor mobility, kitchen tasks, indoor and outdoor domestic tasks, and indoor and outdoor leisure activities (Merkies et al. 2002b). The RHS is administered by an interviewer and the respondent indicates their level of independence in each task, ranging from one, unable, to four, totally independent (where 0 is not applicable). The total score is calculated by summing all the responses, and ranges from nine (maximal limitations) to 36 (no limitations).

1.16.4. Evaluation of outcome tools to measure participation

Advantages

The SF-36 is used widely and has the advantage that scores can be seen in context to normative data for healthy people, indicated by values at the 50th centile, as normality does not always equate to a maximal score on every subscale (Ware and Kosinski 2003). This means scores are interpretable and can be easily communicated. The SF-36 is reliable in a range of patient groups and over several months (median correlation coefficient from 14 studies= 0.8) (Ware and Kosinski 2003) and in neurological and neuromuscular conditions including stroke, MS and amyotrophic lateral sclerosis (ALS) (Anderson et al. 1996; Bourke et al. 2004; Freeman et al. 1996; Hobart et al. 2001; Hobart et al. 2002). The properties of the SF-36 have been investigated in 114 participants with inflammatory PN (Merkies et al. 2002c). Scores were significantly lower than normal population values and physical scales of the SF-36 correlated strongly with strength (MRC sumscore), and activity limitations measured by the GBS disability score, supporting its validity (Merkies et al. 2002c). The SF-36 was internally consistent (Cronbach's α ranged from 0.7 to 1) (Merkies et al. 2002c) and summary scores detected changes in clinical status when re-measured in 20 PN patients undergoing treatment or recovery over one year (Merkies et al. 2002c). The responsiveness of all subscales, except pain and health perception, was also excellent (SRM >0.8) (Merkies et al. 2002c). However, differences between changes from treatment, during recovery and those after an exercise intervention may differ meaning similar responsiveness cannot be assumed in the exercise study (Chapter Two).

Although the FLP is less widely used than the SF-36, it has been shown to be appropriate to measure functioning in other neurological conditions (MS) (Hutchinson and Hutchinson 1995). The full FLP has been used to describe function after GBS (Bernsen et al. 1997) but has not been used to measure changes. It provides a richness and depth of data to allow description of a wide range of areas (e.g. social interaction and emotion) which are not measured by other tools, albeit with considerable respondent and administrator burden. Acceptable test re-test reliability has been shown in a range of conditions including ALS and MS (Damiano et al. 1999; Hutchinson and Hutchinson 1995). It has demonstrated concurrent validity in 122 people with stroke, correlating significantly ($r > 0.56$) with other tools which measure community reintegration (Trigg and Wood 2003) and scores were responsive to changes in the functioning of 20 people with MS over six months (Hutchinson and Hutchinson 1995).

The RHS has been recommended by experts in PN for clinical trials (Merkies and Lauria 2006) and it has face validity as it contains items about return to work, socialising and hobbies which are known to be restricted in people with PN (Merkies et al. 2002b). It demonstrated acceptable inter-rater and test re-test reliability ($r=0.93$ and 0.98 respectively) in 113 people after GBS or with CIDP over 12 months, scores were also significantly associated with the modified Rankin scale ($r=0.76$, $n=113$) and could discriminate between groups with different severities of PN (Merkies et al. 2002b). Scores on the RHS were responsive (SRM= 0.8) to change in 20 patients recovering from GBS or undergoing treatment for CIDP (Merkies et al. 2002b). The RHS has also been used to measure changes after an exercise intervention, reflecting significant improvements in 20 people after GBS or with CIDP after 12 weeks of aerobic training (Garssen et al. 2004), which suggests it is appropriate to detect changes in the study of exercise in Chapter Two.

Disadvantages

Participation, by its nature, is influenced by the individual thus it is unlikely that any standard outcome tool will be able to capture all aspects comprehensively. Indeed, the SF-36 measures several areas which are unrelated to participation although it has been considered to indicate participation in PN by others (Ware and Sherbourne 1992; Ware and Sherbourne 1992; White et al. 2007a). Items on the FLP and SF-36 clearly capture data regarding activity limitations and impairments, including continence and pain. Similarly, some items on the RHS measure independence in ADL (e.g. dressing) in addition to participation. However, their use may still be appropriate as other items do assess definite aspects of participation (e.g. hobbies and employment).

Unlike the RHS, the FLP has considerable administrator and respondent burden (Lohr et al. 1996). Several sections of the FLP are likely to be unaffected in people with PN beyond the acute illness in GBS (e.g. alertness) and are not appropriate for chronic inflammatory PN, increasing item redundancy. The FLP has not been evaluated in PN and so its validity, reliability and responsiveness in this group cannot be assumed. Although the SF-36 is quicker to complete than the FLP, it requires considerable time to calculate subscale and component summary scores, increasing administrator burden. There are also limitations of the PCS and MCS scores as changes on a single domain/subscale can be missed because physical components are negatively weighted on the mental summary scale and *vice versa*. This means that isolated improvement in physical or mental function alone could cause apparent worsening of the other summary score (Simon et al. 1998), reducing validity and responsiveness. It is also unclear if the assumptions required to generate the component scores (e.g. acceptable floor and ceiling effects) are satisfied in PN (Hobart et al. 2001). In light of this shortcoming, use of both summary and sub scale components of the SF-36 is recommended (Hobart et al. 2001; McHorney 1998).

In conclusion, whilst some of the tools that were pre-selected for the study of exercise in Chapter Two have been evaluated and used in people with PN, many have not and, in particular, their ability to measure change after an exercise intervention has not been

established. Therefore, their performance was re-evaluated after their use in Chapter Two. The tools used in the study of exercise in Chapter Two are listed in Table 1-1 overleaf.

Table 1-1 Tools selected for the exercise study (Chapter 2)

Construct	Selected tools
Body structure:	
Strength	Fixed dynamometry (knee extensors)
Specific impairments:	
Fatigue	Fatigue severity scale (FSS)
Mood	Hospital anxiety and depression questionnaire (HADS), Beck Depression Inventory (BDI)
Activity limitations:	
ADL	Overall disability sum score (ODSS)
EADL	Health assessment questionnaire disability index (HAQDI)
Specific components of ADL:	
Mobility/Walking	Ten metre walk test (preferred pace and fast as possible)
Participation restrictions	Rotterdam Handicap Scale, Functional Limitations Profile, Medical Outcomes Short Form 36 questionnaire

1.17. Chapter Conclusion

This chapter outlined the clinical features and common problems experienced by people with inflammatory PN. These include muscle weakness, difficulty walking and completing daily activities, and persistent feelings of fatigue. There is limited evidence evaluating exercise in people with PN. Studies in other patient groups indicate that many of these problems could be helped by exercise but only if people with PN can exercise effectively and find an exercise programme practical. Therefore, the first aim of this thesis was to evaluate the practicality and possible effects of a community based exercise intervention for people after GBS and with CIDP. This study is presented in Chapter Two.

Severe experienced fatigue reduces physical functioning and adds to activity limitations in people with PN. Some reports show that fatigue is reduced after exercise interventions but the mechanism by which regular exercise reduces fatigue is not known (Garssen et al. 2004; Garssen et al. 2005a; Pitetti et al. 1993). If the factors that contribute to experienced fatigue could be elucidated, targeted interventions, such as exercise, could be developed to reduce the severity and effects of experienced fatigue in people with PN. Therefore, the second aim of this thesis was to describe and investigate the nature of experienced and physiological fatigue in people with inflammatory PN. This investigation is presented in Chapters Five and Six.

This thesis required a range of outcome tools to describe functioning and evaluate change. The outcome tools used in this thesis have been critically evaluated in this chapter. Some have previously had their properties established in people with PN, but the majority have not. After use in the exercise study (Chapter Two), three tools (ODSS, Physiological Cost Index and Walk-12) were refined and re-investigated in greater detail in order to determine their suitability for future studies of exercise in people with PN (Chapters Three and Four).

A summary of the key conclusions and areas for future work are presented in Chapter Seven.

Chapter 2. An investigation of exercise in inflammatory peripheral neuropathy

2.1. Summary

The aim of the study in this chapter was to investigate the practicality of a 12 week community based unsupervised exercise programme for the management of activity limitation and wider health in people several years after Guillain-Barré Syndrome (GBS) or with stable Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP).

Sixteen people with GBS (n=10) or CIDP (n=6) and 10 healthy sedentary volunteers undertook a thrice weekly exercise programme comprising aerobic, strengthening and functional exercises for 12 weeks in their local community. Adherence and practicality of the programme were measured using exercise diaries and from participant report. All participants were assessed at baseline and after the intervention (12 weeks); PN participants were also assessed six months after completing the intervention. Changes in activity limitations from baseline were measured using the Overall Disability Sum Score (ODSS). Secondary outcomes of wider health status, participation and extended activities of living were measured using the Short-Form 36 questionnaire (SF-36), Functional Limitations Profile (FLP), Rotterdam Handicap Scale (RHS) and Health Assessment Disability Index (HAQDI) whilst experienced fatigue was measured using the Fatigue Severity Scale (FSS).

Fourteen of 16 PN participants and 8 out of 10 healthy people completed the intervention. Reasons for not completing the programme were not related to exercise. Ten PN participants stated that they continued to exercise six months after the intervention. There were significant improvements in activity limitations after the intervention (mean change in ODSS scores: -1; 95% Confidence Interval (CI): 0 to -1.5) and at six months (mean change: -1; 95% CI: -0.5 to -1.5; $p \leq 0.05$). Wider health status and participation were significantly improved after the intervention in PN participants (mean change, 95% CI; SF-36 Physical Component Score (PCS): 5.8, 2.2 to 9.4; FLP: -4.9, -0.8 to -8.15; RHS: 1, 0 to -2.5 all at $p \leq 0.05$) but the HAQDI was not significantly different from baseline (-0.6, -0.07 to 0.32). The FSS demonstrated a significant improvement in fatigue (mean change: -0.6, 95% CI: -0.17 to -1.2) and the SF-36 PCS remained significantly improved at six months. Healthy participants demonstrated significantly reduced fatigue (FSS mean change: -0.6, 95% CI: -0.2 to -1.2) after the intervention but no other outcomes were significantly different from baseline.

The findings demonstrated that individually prescribed community based exercise was practical and well tolerated. Due to the absence of a non-exercising patient control group and rater blinding, the results must be interpreted with appropriate caution. Although the changes observed could not be confidently attributed to exercise, they suggest that the intervention reduced activity limitations for participants with inflammatory PN.

The study in this chapter has been published and is appended to this thesis:

Graham, R.C., Hughes, R.A.C, White, C.M. A prospective study of physiotherapist prescribed community based exercise in inflammatory peripheral neuropathy J Neurol. 2007 Vol. 254 p 228-235.

2.2. Background

Residual signs and symptoms of weakness, altered sensation, pain and fatigue contribute to persistent activity limitations, altered social status and reduced independence for between 20 to 80% of people after GBS or with CIDP (Bernsen et al. 1997; Bersano et al. 2005; Forsberg et al. 2004; Gorson et al. 1997; Lennon et al. 1993; Merkies et al. 1999). Such chronic disablement can result in a sedentary lifestyle, leading to increased health risks such as obesity, cardiovascular disease and poor mental health (McDonald 2002; Santiago and Coyle 2004).

Narrative and systematic reviews of the current evidence in other neurological conditions have concluded that regular exercise reduces activity limitations, maximises functioning and promotes independence, as discussed in Section 1.9.2 in Chapter One (McDonald 2002; Smidt et al. 2005; Teixeira-Salmela et al. 1999; White et al. 2004). A panel of invited exercise experts and the American Heart Association also state that exercise improves general health, well-being and reduces the health risks associated with inactivity (Kesaniemi et al. 2001). These benefits might also occur in people with activity limitations due to inflammatory PN if they can exercise safely and effectively.

However, potential barriers to exercising for people with PN include the sequelae of GBS or CIDP, such as fatigue, pain, altered proprioception and sensation, muscle weakness and the risk of injury (described in Section 1.5 of Chapter One). Some people with persistent activity limitations do not exercise regularly as they find it difficult and cannot access appropriate support (Rimmer et al. 2004; Rimmer 2005b). These factors may deter people with PN from either commencing or continuing with an exercise programme despite the likely health benefits. Although some of these factors have been addressed by supervised exercise programmes at centralised locations, exercise based in the community is more acceptable as participants are free to choose the location and time that they exercise, promoting adherence (Ashworth et al. 2005). Difficulties accessing transport experienced by some people with inflammatory PN would also make attendance at a centre based programmes difficult and so reduce participation (Merkies et al. 2002b).

White et al. (2004a) found three controlled studies investigating exercise in people with PN that conformed to the majority of the inclusion criteria for their systematic review (Lindeman et al. 1995; Richardson et al. 2001; Ruhland 1997). They found evidence of low to moderate quality to support the effectiveness of progressive resistance training to increase strength in trained muscles (Lindeman et al. 1995; Ruhland 1997; White et al. 2007a) but there was insufficient evidence to judge the effect of aerobic training or to evaluate the effect of exercise on activity limitations. All studies in the review were at high risk of bias due to inadequate or unclear randomisation and allocation concealment, and lack of rater or participant blinding. Although White et al. (2007a) stated in their review "...exercise programmes aimed at strengthening muscles are feasible in people with peripheral neuropathy..." (p9), this statement was based upon evidence from a small number of people with different types of PN and did

not consider the possible complications of undertaking aerobic, or a combination of aerobic and strengthening training, nor if exercise was supervised or not. Two uncontrolled studies in PN, not included in the review, reported that exercise improved fatigue and cardiovascular fitness, but these results could not be directly attributed to exercise due to limitations in their design (Garssen et al. 2004; Pitetti et al. 1993).

The deficits in the current evidence base indicate that high quality randomised controlled trials are needed to demonstrate the effect of exercise in PN (White et al. 2007a). However, it is not known how many participants would be needed to provide sufficient statistical power and the low prevalence of GBS and stable CIDP makes recruitment of enough local prospective participants unlikely. Whilst other designs, such as a delayed intervention or cross over trial may overcome some of the complications of recruitment, the nature of the design would prevent long term measurements of effects attributable to the intervention (Sim and Wright 2000). These limitations indicate that a multi-centred, potentially international, trial would be required to recruit sufficient participants. This is outside the scope of this thesis. However, the ability of people with PN to exercise safely and effectively without supervision has not been established and data are needed to inform the design of a future trial. Therefore, the study in this chapter investigated the practicality (defined as the ability to achieve independent exercise in the community) and potential benefits of an unsupervised community based programme for people with inflammatory PN. These data were also used to ascertain the suitability of outcome tools for other studies in this thesis and will provide data to inform a future controlled trial.

2.3. Aims and Objective

The objective of the investigation was to evaluate the practicality and possible effects of a community based exercise intervention for people after GBS or with CIDP.

The specific aims were:

1. to establish the practicality of a 12 week, community based exercise programme for people with stable motor PN, either at least 12 months after GBS or with CIDP that has been stable for more than six months,
2. to describe and evaluate any changes in activity limitation, participation and functioning of PN participants immediately and six months after completion of the exercise programme.

2.4. Method

A prospective, longitudinal quasi-experimental design was utilised to achieve the aims of this investigation (Sim and Wright 2000). Participants with inflammatory PN were recruited in response to advertisements on the Guillain-Barré Syndrome support group website (www.gbs.org.uk) and magazine ('Reaching Out'), and from the outpatient Peripheral Nerve clinic at Guy's Hospital, London. Volunteers were eligible for inclusion if they were at least 12 months after the nadir of GBS, or had stable CIDP with no self reported change in symptoms or medication in the previous six months. A steering committee (Appendix One) initially developed the design of the trial, selected outcome tools and exercise frequency. The Guillain-Barré Syndrome support group (GBSSG) provided funding for equipment and participant travel expenses.

A non-matched control group of healthy, sedentary participants from staff and students of King's College London was recruited by email advertisement. These participants had no health problems but had not taken part in regular exercise for at least six months. They were included to provide normative values for comparison to PN participants, and to establish that the prescribed intensity and type of exercise was practical and effective in a healthy population.

History taking, clinical examination and a resting electrocardiogram were performed to ensure that all participants conformed to the inclusion criteria in Table 2-1, and had no complications (including autonomic dysfunction in people with PN) that could affect their safety when undergoing an exercise test or exercising in the community (Fletcher et al. 2001).

Medical screening by a neurologist confirmed diagnoses based upon published criteria (Asbury and Cornblath 1990; Hughes et al. 2001; Joint task force of the EFNS and the PNS 2005; Nicolas et al. 2002).

Participants were assessed by a chartered and HPC registered physiotherapist (the author) to identify impairments, functioning and any risks of musculoskeletal injury when exercising. Participants with PN were provided with orthotics, if indicated, to ensure safe exercise. Practical concerns including the ease of exercise in a home or gym environment were discussed, and appropriate equipment was obtained to facilitate effective and safe exercise if necessary.

All participants gave written informed consent and ethical approval was granted from Guy's Hospital and King's College London research ethics committees in accordance with the 1964 Declaration of Helsinki.

Table 2-1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Aged over 18 years	Any cardiovascular, orthopaedic or other neurological condition which may affect the safety of exercise and outcome
Willing to exercise thrice weekly for approximately one hour per session for three months	Pregnant women or those who think they might be or plan to become pregnant
Good command of the written and spoken English language.	Current regular immunoglobulin or plasma exchange treatment
*A confirmed diagnosis of stable motor peripheral neuropathy including GBS at least one year after nadir and stable CIDP (defined as no change in self reported disability, symptoms or medication for the previous 6 months).	

* these criteria were not applicable for healthy participants.

2.4.1. Sample size

Data were not available to calculate the sample size needed for this study. However, the sample size was informed by a previous study of a combined exercise intervention undertaken in a similar patient group which included 14 PN participants, suggesting that this number would be the minimum needed for the current study (Ruhland 1997). The size of the sample was also influenced by the availability of suitable participants who could travel to London for testing during the study period.

2.4.2. Measurement

A wide range of outcome tools were used to measure different aspects of functioning in this patient group. This attempted to ensure all pertinent changes which might be elicited by the intervention were adequately reflected. These tools have been described in Chapter One.

All participants attended for two baseline measures of outcome, approximately one month apart, before beginning the exercise programme. This was to allow familiarisation with testing procedures and to provide data to establish pre-intervention stability. All participants were asked to continue their usual activities between baseline assessments.

All measures were repeated at halfway (18 sessions, six weeks) and on completion of the programme (36 sessions, 12 weeks) in both groups. People with PN were also re-tested six months after completing the programme.

With the exception of activity limitations, participation restrictions and disease specific outcome tools, healthy participants completed the same assessment and exercise programme as PN participants.

All measurements took place in a quiet and comfortable room. Participants were instructed not to eat for two hours before the assessment and to wear loose clothing and appropriate

footwear, ideally trainers. All questionnaires were administered in a random order before completing any physical measurements in attempt to standardise arousal. The order of physical tests was kept the same on each testing occasion, with the exercise test being conducted last to minimise the effect of fatigue. All data were collected by a single unblinded rater (the author).

Baseline measurements and findings from the subjective and objective physiotherapy assessment were used to inform the design of the exercise programme, which was tailored to each participant's ability and personal goals. All participants completed aerobic and strength training with individual functional exercises (described on page 74). The programmes of the healthy participants were designed to be similar to PN participants.

2.4.3. Assessment of practicality and acceptability of the programme

The practicality and acceptability of the exercise programme were assessed by counting the number of responses to recruitment adverts, by monitoring participant report and exercise adherence from exercise diaries.

The participant and investigator maintained regular telephone contact throughout the duration of the programme, to investigate and address any practical issues. Participants were asked if they had encountered any difficulties with the exercise programme, or had experienced any unwanted or unpleasant side effects during telephone conversations and reassessment visits. Participants were not directly questioned about the presence or absence of specific, named problems to avoid biasing their report (Ruhland 1997), but they were instructed to report any concerns to the investigator. These were noted and appropriate advice and adaptations made.

Participants were asked to record information after every exercise session in an exercise diary to monitor exercise adherence. Heart rate monitors which recorded the time, date, heart rate and duration of exercise were provided to all participants to judge adherence to the aerobic exercise component of the programme (as described in Section 2.4.6). These data were downloaded by the investigator during and on completion of the intervention.

Semi structured, informal interviews were used by the investigator to ascertain the views of the participants about each component of the programme and their overall appraisal of the intervention on completion of the programme. These were also repeated at six months in PN participants. Participants were asked open ended questions about how practical they found each aspect of the exercise programme and any differences they had noticed since exercising. They were asked one closed question about how they felt relative to baseline (better, worse or the same). At six months, questions regarding the effectiveness of the programme were replaced with open questions regarding continued exercise. An extra question regarding changes in health since completion of the programme was also included.

2.4.4. Primary outcome tool

The primary outcome was alteration in activity limitations which was measured using the total score on the disease specific overall disability sum score (ODSS) questionnaire (Merkies et al.

2002a) (Page 51). Upper and lower limb scores were considered separately in addition to evaluation of the total scores.

2.4.5. Secondary outcomes

Secondary outcomes aimed to measure a range of parameters including participation, mental health, fatigue and extended activities of daily living (EADLs). Other measures were also used to assess walking ability, knee extensor strength, cardiovascular fitness and general activity levels.

Extended Activities of Daily Living

Extended ADLs were measured using the Health Assessment Questionnaire Disability Index (HAQDI, Page 53) (Bruce and Fries 2003). This questionnaire has eight categories which measure the respondent's perception of difficulty and assistance needed to complete a range of ADL and EADLs.

Participation

Changes in scores on the SF-36 questionnaire subscales and physical and mental component summary scores, Rotterdam handicap scale (RHS) and functional limitations profile (FLP) were used to evaluate alterations in participation and wider health status (Hutchinson and Hutchinson 1995; Merckies et al. 2002b; Merckies et al. 2002c; Ware and Sherbourne 1992). As noted in Chapter One (Page 56), these tools also measure other aspects of functioning in addition to participation, which was considered when interpreting the results.

Experienced fatigue and mood

Fatigue was measured on the fatigue severity scale questionnaire (FSS, Page 46) (Krupp et al. 1989; Merckies et al. 1999). The Hospital Anxiety and Depression scale (HADS, Page 49) was used to measure anxiety and depression, and the severity of depression was measured with the Beck depression inventory (BDI, Page 49) (Beck et al. 1996; Zigmond and Snaith 1983).

Walking

The walking speed of all participants was assessed by measuring the time taken to walk ten metres, both at a preferred pace and as fast as safely possible (Salbach et al. 2001; van Loo et al. 2003) as discussed on Page 55.

The physiological demand or energy cost of comfortable walking was measured using the physiological cost index (PCI) (MacGregor 1979; MacGregor 1981) and modified PCI (mPCI). The properties of the PCI and mPCI were investigated in Chapter Four (Page 143).

Participants were fitted with heart rate monitors (Polar, Finland) and rested in sitting until their heart rate had reached steady state (Corry et al. 1996; Ijzerman and Nene 2002). Steady state heart rate was attained when readings of heart rate taken one minute apart were within five beats of each other (Bailey and Ratcliffe 1995). Participants then walked at their comfortable pace around a 20 metre figure of '8' track. Heart rate was recorded at the end of each minute.

Participants continued walking for at least four minutes and until heart rate had reached steady state. The distance walked was recorded. The PCI and mPCI were calculated from (MacGregor 1979):

$$\text{PCI (beats m}^{-1}\text{)} = \frac{\text{Working HR} - \text{Resting HR (beats min}^{-1}\text{)}}{\text{Speed (metres min}^{-1}\text{)}}$$

$$\text{mPCI (beats m}^{-1}\text{)} = \frac{\text{Working HR (beats min}^{-1}\text{)}}{\text{Speed (metres min}^{-1}\text{)}}$$

PCI=physiological cost index, mPCI= modified physiological cost index, HR= heart rate

Strength

Peak isometric linear knee extension force (Newtons) was measured in both legs using fixed dynamometry (discussed on Page 45). Both legs were tested in a random order on each occasion. These data were re-measured on completion of the programme and at six months (in PN participants).

The testing position and a more detailed method are presented in Appendix Two. In brief, participants were positioned in sitting with the knee flexed to 90° and a padded cuff connected to a strain gauge was positioned above the medial and lateral malleoli. Participants were instructed to straighten their knee maximally and given vigorous, standardised verbal encouragement throughout (McNair et al. 1996; van der Ploeg and Oosterhuis 1991). If force production continued to increase on the third contraction, more measurements were taken until force did not increase further to ensure adequate familiarisation.

To inform the design of each individual's exercise programme, isometric muscle strength was measured using a hand held dynamometer and graded using the MRC score in the following pairs of muscles: shoulder abductors, elbow flexors, wrist extensors, hip flexors and ankle dorsiflexors using hand held dynamometry (Andrews et al. 1996; Medical Research Council 1976). Hand grip was measured using a hydraulic hand grip dynamometer (Jamar, LaFayette, Indiana, USA). If participants were unable to securely hold the Jamar dynamometer, an inflatable pressure device was substituted (KCI Mediscus, UK). These data were only used in addition to physiotherapy assessment findings to identify muscles suitable for training and so are not presented here.

Exercise testing

Healthy and PN participants completed a symptom-limited graded exercise test on an upright bicycle ergometer (Monark 818E, Monark, Sweden) at each measurement session, to establish peak exercising heart rate. This was used to calculate the exercise intensity for the aerobic component of the exercise programme. Peak and total workload (Watts) produced

during the exercise test were also recorded to assess the effectiveness of the aerobic training component of the intervention.

Cycle based exercise testing was used in preference to other forms of exercise, such as treadmill or arm ergometry, to standardise testing and because it was suitable for all participants as it minimised difficulties with balance or hand grip (American College of Sports Medicine 1995).

Before starting the test, participants rested for ten minutes. Measurements of heart rate using a heart rate monitor (Polar, Finland) and blood pressure were recorded using an electronic sphygmomanometer (Omron, HEM-757) (American College of Sports Medicine 1995).

After resting, participants were seated comfortably on the exercise bike and the seat and pedals were adjusted to allow 5 to 10° of knee flexion when the foot was at the lowest point and to ensure that the foot remained in contact with the pedal. The foot was secured onto the pedal using a toe strap and extra Velcro straps if necessary.

All participants were instructed to maintain a loose grip on the handle bars and completed three minutes of cycling against no resistance prior to beginning the test (American College of Sports Medicine 1995). Participants cycled at a constant rate of 60 revolutions per minute throughout the warm up and test. This was shown on a digital display mounted on the handlebars. On completion of the warm up, the workload was increased by 30 Watts every minute (Mullis et al. 1999). This protocol was selected as it allowed gradual increases in workload but did not require participants to exercise for long periods, which is recommended to reduce the risk of adverse events in deconditioned individuals (Pollock et al. 1998). Participants were encouraged to cycle for as long as they could. Blood pressure was measured every two minutes and heart rate was monitored continuously.

The primary indication to end the exercise test was the participant's desire to stop or the speed of cycling decreasing below 60 revolutions per minute for more than five seconds (judged by the investigator). Other indications to end the test included:

- a drop in systolic blood pressure >10 mmHg despite an increase in workload, or values of systolic blood pressure > 220 mmHg and diastolic pressure >115 mmHg
- pain
- increasing nervous system symptoms (e.g. near-syncope, dizziness),
- signs of poor central or peripheral perfusion (e.g. pallor) (Gibbons et al. 2002)

On completion of the test, participants continued cycling for three minutes to cool down, at a self-selected speed against no resistance (American College of Sports Medicine 1995). Heart rate and blood pressure was monitored after the exercise test for five minutes or until they returned to near pre-test values.

The highest level of resistance at which participants were able to complete an entire minute was defined as the peak workload (Watts). Additionally, the total workload (Watts) was calculated by summing the work done at each level of resistance.

2.4.6. Design of the exercise programme

The design of the exercise programme was informed by recommendations and literature for healthy people and those with other neurological conditions. Whilst every participant's exercise programme followed a similar structure, each was individually tailored to address each participant's main functional impairments and activity limitations. This was informed by assessment and physiotherapy examination. All participants exercised in an unsupervised community setting, either at home or at their local gym. Each exercise session was designed to take approximately one hour to complete. This duration appears common in exercise programmes and is considered practical for most individuals to undertake regularly (American College of Sports Medicine 1995).

As the programme was unsupervised, participants could choose the time and day that they exercised, but were advised to leave at least 24 hours between each session. They were instructed to avoid alcohol and large meals before exercising, to drink water throughout the exercise session and to postpone exercising if they were unwell (American College of Sports Medicine 1995). Participants were also instructed to cease exercise if they had any pain or practical concerns and to contact the investigator with any queries or problems.

At each session, participants wore a heart rate monitor to guide the intensity of warm up, aerobic training and warm down. The heart rate monitor also recorded and stored details of the time, date, duration of exercise and heart rate during each exercise session. Additionally, they also used the 6-20 Borg scale of perceived exertion to guide effort (American College of Sports Medicine 1995; Borg 1982).

Training frequency and duration

Participants were asked to complete three exercise sessions every week for 12 weeks (36 sessions). Training at this frequency has been shown to produce significant increases in strength and aerobic fitness in healthy adults (Haskell et al. 2007; McLester et al. 2000). This duration was chosen to ensure there was adequate time to demonstrate changes in strength, fitness and activity limitations even if some initial sessions had to be completed at a lower intensity as reported by others (Ruhland 1997). This duration and frequency also appeared feasible for participants to complete in a study of exercise in 20 people with PN (Garssen et al. 2004) and are recommended for the novice exerciser (American College of Sports Medicine 1995; Haskell et al. 2007).

If any exercise sessions were missed, participants were encouraged to try to incorporate extra sessions within the 12 week period but additional sessions were added at the end of the programme if necessary.

Warm up

A ten minute warm up, working below 60% of peak heart rate, determined from the exercise test or working at an intensity of “very light (9)” to “fairly light (11)” on the Borg scale, was performed at the start of exercise session (Borg 1982). A warm up of this nature is recommended to reduce the risk of injury (American College of Sports Medicine 1995; Fradkin et al. 2006).

The type of exercise modality (e.g. walking, cycling) for the warm up and aerobic training was chosen by the participant and physiotherapist (the investigator) after consideration of practical issues.

Participants progressed directly from the warm up to the aerobic exercise component of the programme.

Aerobic training

Each participant exercised for 20 minutes at an intensity of 60-85% of peak heart rate which is recommended to improve cardiovascular fitness (American College of Sports Medicine 1995; Haskell et al. 2007). Upper and lower limits of heart rate during the aerobic exercise were pre-programmed into heart rate monitors, which also stored heart rate and duration of exercise. Participants used the monitors to guide the intensity of exercise and were advised how to increase or decrease heart rate to remain within their training zone. Participants could also use the Borg scale to guide exertion, working between 12 and 16, which is reported to be approximately equivalent to 60-89% of maximum heart rate for healthy individuals, although this has not been established in PN (American College of Sports Medicine 1995; Fletcher et al. 2001).

If participants were initially unable to exercise continuously for 20 minutes, the duration of exercise was increased incrementally over several exercise sessions.

Strengthening Exercise

After completing the aerobic component of the programme, participants performed several isometric strengthening exercises.

Resisted maximal isometric contractions were used as a static contraction was easy for participants to replicate safely without supervision, limited the risk of injury and indicated the largest strength gains as participants were tested isometrically (Aitkens et al. 1993; Khouw and Herbert 1998; McGlynn 1972). Participants held each contraction for ten seconds which is reported to be a sufficient duration to strengthen muscles, if frequency and intensity are adequate (Agre et al. 1997; Bandy and Hanten 1993; Khouw and Herbert 1998; Kubo et al. 2001; Weir et al. 1995). They were instructed to breathe regularly throughout to limit rises in blood pressure (O'Connor et al. 1989).

Strength exercises were targeted at weaker muscles identified by dynamometry and physiotherapy assessment. For participants exercising at home these were performed against resistive bands (Theraband®, USA). If participants were exercising at their local gym, weight machines were set to provide sufficient resistance to allow isometric muscle work. Muscles

that were below MRC muscle score grade two (Medical Research Council 1976) were not targeted for specific strengthening exercises. Severely weak muscles have not shown increases in strength after specific training in neuromuscular disease (Lindeman et al. 1995; Milner-Brown and Miller 1988) and, as exercise was unsupervised and used limited equipment, it was not possible to directly exercise these muscles in a way that could be effective.

Number of repetitions and sets

Participants gradually increased the number of repetitions and sets they performed under the instruction of the physiotherapist, as they progressed through the initial exercise sessions, building to a maximum of three sets of ten repetitions (Galvao and Taaffe 2004; Wolfe et al. 2004). Eight to 12 repetitions are recommended for the novice exerciser to increase both muscular strength and endurance (American College of Sports Medicine 1995). This number of repetitions, appears practical and has been shown to increase strength (Braith et al. 1989; Starkey et al. 1996; Szeto et al. 1989; Weir et al. 1995). The added benefit of three compared to one set of repetitions remains controversial (Galvao and Taaffe 2004) but as contractions were isometric and did not require an increase in load, increasing the number of sets performed provided some feedback on progress to participants.

Other exercises

Several functional exercises were also included for each participant, informed by the findings from their physiotherapy assessment. The types of functional exercise used included balance training, moving from sitting to standing from progressively lower surfaces, dynamic bilateral squats, bridging (lifting the pelvis whilst lying supine with legs bent) or postural exercises. These were included as targeted exercises have significantly improved balance in people with PN and significantly improved activities and performance in stroke survivors and the elderly (American College of Sports Medicine 1995; de Vreede et al. 2005; Eng et al. 2003; Richardson et al. 2001).

Stretches and cool down

Each session of exercise was ended by a five minute cool down which consisted of walking or gentle cycling. An adequate cool down is reported to decrease muscle soreness and return heart rate to normal ranges, reducing the risk of cardiac complications (American College of Sports Medicine 1995; Fletcher et al. 2001; Reisman et al. 2005; Roberts and Wilson 1999). Participants were guided to work at an intensity of “very light” to “fairly light” on the 6 to 20 Borg scale (Borg 1982). Stretches for the major muscle groups utilised in the programme (quadriceps femoris, hamstrings and gastrocnemius muscles) were completed to reduce the risk of soft tissue injuries. Stretches were held at the point of mild discomfort for a count of 15 seconds and were repeated three times (American College of Sports Medicine 1995; Roberts and Wilson 1999).

2.4.7. Analysis

Normality of data

Raw questionnaire data were assumed to be non-parametric, due to the non-linear nature of the scales. Transformed questionnaire and all other data were examined for normality using Kolomogorov Smirnov tests and examining frequency histograms. Parametric and non-parametric statistics were then used.

Baseline measurement

Differences between the two baseline measurements, assessed a month apart, in PN and healthy groups were examined using paired t or Wilcoxon tests. If significant within group differences were found, a 95% range was calculated to provide an indication of the variability of repeated measurements at baseline and to indicate the range that should be exceeded for a change in scores to indicate a genuine change in functioning (Altman 1991). It was calculated using:

$$95\% \text{ range for change} = 1.96 \times SD_{(y1-y2)}$$

Where: SD= standard deviation, y1=score at baseline one, y2=score at baseline two.

Differences between groups

Differences between healthy and PN groups were examined at baseline using two tailed independent t and Mann Whitney tests.

Practicality and acceptability

Practicality : The report of successful completion of exercise sessions by participants was used to judge the practicality of the programme. Any difficulties with equipment, exercises or with components of the programme were noted. Answers to the semi structured interview questions at the end of the programme and at six months were recorded with participant comments about how easy or difficult they found the exercises.

Acceptability: This was ascertained by participant report throughout the programme and on the semi structured interview in which participants were asked to comment on the frequency, intensity and duration of the programme.

Adherence

Exercise adherence was measured by counting completed exercise sessions detailed in participants' diaries. The time to complete 36 sessions was also noted.

Heart rate records stored on the heart rate monitor were used to judge adherence to the aerobic component of the programme. They were downloaded at half way and at the end of the programme to analyse the number of sessions completed and the time spent working within the heart rate training zones during the aerobic training component.

Changes after the intervention

Differences in measurements between baseline and completion of the exercise programme, and between baseline and six month follow up, were examined using one way repeated measures ANOVA or Friedman's (non-parametric repeated measures) tests. Significant differences on repeated measures tests were further examined to determine the time at which differences occurred (between baseline and end of the programme, and baseline and six months) using two tailed paired t or Wilcoxon tests. No adjustments were made for multiple comparisons (Campbell et al. 2000; Perenger 1998).

Confidence limits (95%) of the average (mean or median) change were calculated for all measures.

Retrospective statistical power was calculated for a parametric outcome tool (the SF-36 questionnaire physical component summary score) after exercise and at six months (Huck 2004a).

Properties of outcome tools

Floor and ceiling effects, defined as the percentage of the participants who achieve the worst and best possible scores respectively, were judged from baseline measurements in PN participants. These are recommended to be below 15% (McHorney and Tarlov 1995).

As some data were not parametric and did not conform to a normal distribution, responsiveness was calculated using distribution free method of calculation (Hamilton 1991). This allowed comparison between all outcome tools analysed. It is calculated from:

$$\text{Responsiveness} = \frac{\text{median change in scores}}{\text{Interquartile range of change}}$$

A higher score indicates greater responsiveness to change.

Responsiveness was examined for changes from baseline to 12 weeks and baseline to six months. The mean of the responsiveness after the intervention and at six months was used to examine the overall responsiveness of each tool.

All data were analysed using SPSS© software (SPSS Inc. version 11.5.1.). Significance for all tests was set at $p < 0.05$ (two tailed).

2.5. Results

2.5.1. Participants

Forty one people responded to the adverts in the GBSSG website, 'Reaching Out' magazine and the neuromuscular clinic at Guy's Hospital.

Sixteen people were eligible for inclusion. Reasons for non-inclusion are listed in Table 2-2.

Table 2-2 Reasons for non inclusion

Reason for non-inclusion	Number of people
Lived too far away	13 (3 non-UK residents)
Did not have diagnosis of CIDP or GBS	5
Co-morbidities affecting exercise	1
Instability of CIDP	6

Two participants in each group did not complete the programme. One PN participant changed medication just after starting exercise and was excluded. The second had to leave the UK for several months. One healthy participant left the study after halfway for personal reasons unconnected to exercise. The second was excluded after missing several exercise sessions after sustaining a minor ankle sprain unrelated to exercise. Data were analysed from remaining participants in each group (n=14 and n=8).

Full six month follow-up data were available for 13 PN participants as one person was unable to attend for physical tests after moving away. All questionnaire and interview data were completed via post and over the telephone for this participant. No six month follow up was performed in the healthy group.

Two PN participants were provided with flexible bilateral ankle foot orthoses (Bioskin Trilok, Cropper Medical Incorporated, USA) after initial assessment. Participant characteristics are displayed in Table 2-3.

Table 2-3 Characteristics of participants who completed the exercise programme

	Peripheral neuropathy group (n=14, 4 females)	Healthy group (n=8, 3 females)	p
Mean age in years (range)	52.4 (27.9-74.1)	47.5 (32.1-54.2)	ns
Weight (Kg)	79.7 ±15.5	72.4 ±12.7	ns
Height (metres)	168.4 ±7.6	171.9 ±10.3	ns
Body Mass Index (kg m ⁻²)	28 ±4.5	24.3 ±1.9	0.02
Diagnosis	GBS: 10, CIDP:4		
Time since diagnosis (years, range)	5.9 (0.67-17.6)		

All values are mean ± SD unless otherwise stated. From GBS participants, 9 had AIDP, and 1 had Acute Motor and Sensory Axonal Neuropathy (AMSAN). All CIDP participants had typical CIDP.

2.5.2. Practicality, acceptability and adherence

In the PN group, four participants exercised at their local gym and ten exercised at home. The aerobic and strengthening components of individual PN participants programmes are shown in Table 2-4 . One participant was unable to use the upright exercise bike for testing so used a modified recumbent cycle (Viva 2, Medimotion, UK) for exercise testing and for training at home. Seven healthy participants exercised using local gym facilities whilst one exercised at home. All healthy participants performed a range of strengthening exercises which were identical to those used in the PN group. Four healthy participants trained aerobically by walking or running, three cycled and one rowed.

No participants left the study for reasons associated with the exercise intervention.

Based on self report diaries, people with PN completed a mean ±SD of 37 ±3 sessions over 3.67 ± 1.4 months. Healthy people reported completing 36 sessions ±1 during 3.5 ± 0.2 months.

The majority of participants did not manage to record heart rate data for all sessions successfully so these data could not be used to judge adherence. Session recordings were also sometimes affected by interference from heart rate monitors used by other exercisers and electrical equipment in several participants who exercised in the gym. Therefore, adherence was based upon self report alone. All participants reported they were able to complete 20 minutes of aerobic training and three sets of ten repetitions of strengthening exercises by four weeks after commencement of exercise.

One PN participant chose to perform the aerobic and strengthening components on different days because of time restrictions. All other participants completed the entire programme on the same day, reporting it to take about one hour.

Table 2-4 Training methods for PN participants

Participant number	Aerobic exercise	Strengthening exercises
1	Cycling	Knee extensors & flexors, ankle dorsiflexors
2	Cycling	Knee extensors & flexors, ankle dorsiflexors
3	Cycling	Knee extensors & flexors
4	Walking	Knee extensors & flexors, shoulder abductors
5	Cycling	Knee extensors & flexors
6	Walking, stair climbing	Knee extensors & flexors, elbow flexors, ankle dorsiflexors
7	Walking	Knee extensors & flexors, hand grip
8	Walking	Knee extensors & flexors, ankle dorsiflexors
9	Cycling	Knee extensors & flexors, ankle dorsiflexors, elbow flexors
10	Walking	Knee extensors & flexors, ankle dorsiflexors
11	Cycling*	Knee extensors & flexors
12	Cycling, exercise in water	Knee extensors & flexors, elbow flexors
13	Walking	Knee extensors & flexors, elbow flexors
14	Rowing	Knee extensors & flexors, ankle dorsiflexors

* denotes use of recumbent exercise bike for testing and training

Participant report

After being shown their exercises, provision of equipment and an exercise booklet, all participants reported completing their programme with no practical difficulties. Seven PN participants and four healthy people reported minor muscle ache and stiffness after exercise. Symptoms disappeared within 48 hours and participants reported that symptoms were only apparent in the first half (18 sessions) of the programme. These participants also reported that these symptoms did not prevent normal functioning and exercise. No other symptoms or injuries were reported to the investigator during or after the intervention.

On completion of the intervention, all reported that the programme was realistic and practical to complete. From contact with the investigator during the programme, there were no reported differences in practical difficulties or unwanted effects of exercise encountered by GBS or CIDP participants. Contact between the physiotherapist (the investigator) and participants occurred approximately once weekly, and became much less once participants became familiar with the programme.

Several of the ten PN participants who exercised at home reported that this added flexibility to the programme, improving their adherence to exercise. Conversely, the four PN and seven healthy participants who chose to use local gym facilities said that this allowed time to exercise without distraction and increased their ability to exercise regularly. These PN participants reported that the gym equipment was straightforward to use after initial induction by gym staff and the author. Some participants reported that dynamic contractions for strengthening, rather

than isometric exercises, would allow them to judge their improvement and provide motivation. This indicates that the use of isometric contractions may have decreased their adherence to the strengthening component of the programme, although this was not reported.

On completion of the exercise programme, all participants stated that they felt “better”, when asked to rate their health to pre exercise levels; common improvements stated included increased energy and better mood.

At six month follow up, 11 PN participants reported feeling better than prior to starting the exercise programme and three felt they were the same. No-one felt worse than prior to starting the exercise programme. Six participants reported feeling better than when they had completed the programme, four felt unchanged and four felt worse.

Ten PN participants reported continuing regular exercise at six months, from the four that did not, three felt worse than they did at completion of the programme. Reasons given for not continuing exercise were related to lack of time. Of those that continued exercising, all felt better than prior to starting the programme, six felt better than at the end of the programme, one felt worse and three reported they were unchanged.

2.5.3. Differences between baseline measurements

Peripheral neuropathy group

There were no significant differences between baseline measurements taken four weeks apart (data not presented) within the PN group except for a significant improvement in the scores from the role limitation physical (RLP) subscale of the SF-36 questionnaire (median change= +12.5 points, range= 0-100). The 95% range for change indicated that scores would have to change by more than 69 points to demonstrate an alteration beyond that attributable to variation between baselines.

Healthy group

Healthy participants demonstrated a significant decrease in scores on the FSS at the second baseline, indicating less fatigue (mean decrease= 0.64 ± 0.32). Calculation of the 95% range for change indicated that a change in the FSS scores should exceed 0.62 to indicate an alteration in experienced fatigue beyond baseline variation in this group. The time taken to walk 10 metres at a preferred pace also decreased significantly at the second baseline (7.0 ± 1.1 seconds to 6.7 ± 0.9 seconds, 95% range for change= 0.8 seconds) which could indicate increased familiarisation with the test.

Differences between PN and healthy groups at baseline

The second baseline measurement values were chosen for subsequent within and between group comparisons. This was to minimise any learning effects as, despite familiarisation with the assessment techniques, both groups demonstrated some differences between baseline measurements.

There were several significant differences between healthy and PN groups at baseline. Participants with PN had a significantly greater body mass index (BMI) than healthy volunteers (participant characteristics are shown in Table 2-3). Ten had a BMI greater than 25, indicating they were overweight, and four of these had a BMI over 30, signifying obesity (McArdle et al. 1996). There were no other significant differences in anthropometric variables between healthy and PN participants.

Participants with PN had significantly higher levels of fatigue measured on the FSS and also demonstrated significantly lower energy, physical function and more pain on the SF-36 questionnaire in comparison to healthy participants (shown on Page 86, Table 2-6).

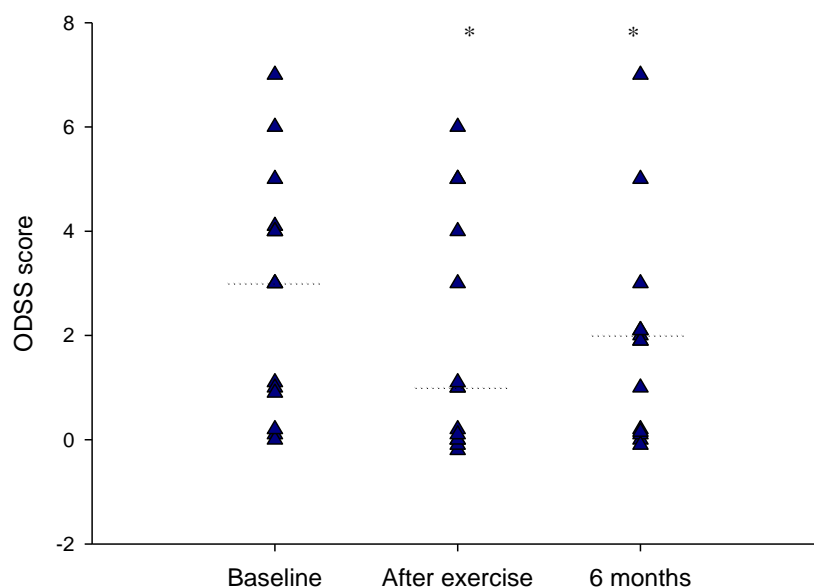
Participants with PN also walked more slowly on both preferred pace and fast 10 metre walk tests (Table 2-7, Page 88). Healthy participants reached a higher peak heart rate on the exercise test, although differences in workload did not reach significance between the groups (Table 2-7).

2.5.4. Changes after exercise

Activity limitation

Activity limitation, the primary outcome evaluated in this study, was significantly improved directly after exercise in the PN group, when measured on the ODSS (Figure 2-1 and Table 2-5). Improvements in both upper and lower limb scores were evident, as shown in Table 2-5.

Figure 2-1 ODSS scores in PN participants at baseline, after exercise and at six months



Each symbol represents one person (n=14). Dotted line indicates median score. * denotes significant difference from baseline at $p<0.05$.

Extended ADL, participation and wider health status

In PN participants, scores on the RHS, SF-36 and FLP were significantly improved after the intervention. Changes on the RHS and FLP are summarised in Table 2-5, alterations on the SF-36 are shown in Table 2-6.

Whilst the physical subscale score on the FLP was not significantly different from baseline, improvements in the psychosocial and total scores reached significance. Total FLP scores remained significantly improved at six months, but RHS scores were not significantly different from baseline at six months.

Extended activities of daily living, measured on the Health Assessment Questionnaire Disability Index (HAQDI), were not significantly improved after the intervention or at six months, as shown in Table 2-5. Scores on HAQDI were low at baseline, indicating minimal activity limitations.

Table 2-5 Changes in activity limitation, EADL and participation restrictions in PN participants after exercise and at six months

Measure	Baseline	Change after exercise	p	Change at 6 months	p
ODSS	3 (0-7)	-1 (0 to -1.5)*	0.02	-1 (-0.5 to -1.5)*	0.008
ODSS UL	1 (0-3)	-1 (0 to -1.5)*	0.02	0 (0.5 to -0.5)	ns
ODSS LL	1 (0-4)	-0.5 (0 to -2)*	0.03	0.5 (0.5 to -1)	ns
FLP Total	9.9 ±8	-4.9 (-0.8 to -8.15)*	0.02	-4.1 (0.32 to 7.7)*	0.03
FLP physical	12.5 ±11.3	-5.3 (-0.4 to 10.9)	ns	-4.5 (-0.2 to 9.1)	ns
FLP psychosocial	8.6 ±7.2	-5 (-1.4 to 8.3)*	0.05	-3.4 (-0.2 to 9.1)	ns
HAQDI	0.25 (0-2.1)	-0.6 (-0.07 to 0.32)	ns	0.07 (-0.19 to 0.13)	ns
RHS	33.5 (26-36)	1 (0-2.5)*	0.05	1 (-3 to 0.5)	ns

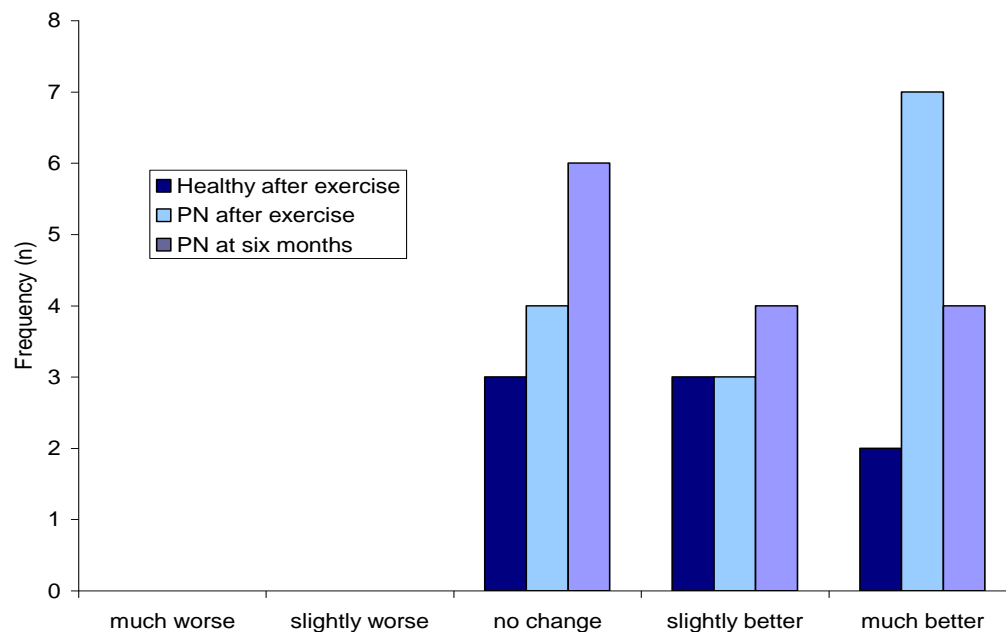
All baseline values are median (range) except for FLP scores which are mean ±SD. All changes after exercise and at 6 months are median change (95% CI) except for FLP, which is mean change (95% CI). ODSS – overall disability sum score, FLP – Functional limitations profile (physical and psychosocial subscales), HAQDI – Health assessment questionnaire disability index, RHS –Rotterdam handicap scale. * denotes significant change from baseline.

After the intervention, the SF-36 PCS scores improved significantly in people with PN, and approached values from a healthy population (50) (Ware and Kosinski 2003). The SF-36 subscales of physical functioning, health perception and energy and vitality subscales of the SF-36 were also significantly improved after the intervention in the PN group (Table 2-6). Both improvements on the PCS and the physical function subscale of the SF-36 were maintained at six months (Table 2-6) and similar changes in outcome were found both for people with CIDP and GBS. There were no significant changes in subscales or PCS in healthy participants.

Health, relative to one year ago, was measured on the ninth subscale of the SF-36 (“health transition”). After the intervention, the PN participants reported health was significantly better

than one year previously, but this was not maintained at six months. After the programme, five healthy people also reported improved health on this subscale but changes in this group were not significant. The perceived change in health for healthy and PN participants is shown in Figure 2-2.

Figure 2-2 Perceived change in health, measured with the SF-36, in healthy and PN participants from baseline to after exercise and in PN participants from baseline to follow up at six months.



Changes in experienced fatigue and mood

Changes in experienced fatigue and mood after the intervention in healthy and PN participants are shown in Table 2-6 (Page 86). After the programme both groups reported significantly improved feelings of fatigue. Experienced fatigue also remained significantly improved from baseline at six months in PN participants. This was echoed by significant increases in the energy and vitality subscale on the SF-36 questionnaire after the intervention in people with PN although this was not maintained at six months ($p=0.06$).

As there were significant differences between baseline measurements of fatigue for healthy volunteers, it was calculated that scores would have to demonstrate a change greater than 0.62 (95% range for change), despite significant improvements, to indicate an alteration in fatigue beyond the variation seen at baseline. This was seen in six of eight healthy people after the exercise intervention.

Overall median anxiety levels were classified as normal throughout the study using cut off values for healthy subjects in the PN group, but would have been classified as mild anxiety if values used in stroke were utilised (Bjelland et al. 2002; Zigmond and Snaith 1983).

Healthy participants demonstrated minimal levels of anxiety and depression throughout the study. At baseline, two PN participants demonstrated severe anxiety, which improved to moderate levels on completion of the programme. Similarly, median depression scores were within the normal range in the PN group, but one person with PN demonstrated severe depression on both the BDI and HADS depression subscale. After the intervention this decreased to moderate levels (Beck et al. 1996; Snaith and Zigmond 1994). As shown in Table 2-6, anxiety and depression were significantly improved after the intervention in the PN group, although significant improvements in depression scores were not maintained at six months.

Changes in strength

All healthy and PN participants trained the knee extensor muscles. In the PN group, mean linear isometric force values were somewhat lower than those found in healthy subjects in this study and reported by others (mean isometric force in dominant leg : 407 N and non dominant leg: 403 N) (Bohannon 1997b). However, the healthy and PN groups were not matched for age or gender in this study, and differences in the method of testing between the current study and Bohannon (1997) limits the validity of these comparisons. Baseline values and changes in isometric strength in this muscle group after the intervention and at six months are shown in Table 2-7 (Page 88).

After exercise, isometric strength in both legs was increased, this reached significance in the right leg of PN participants (mean percentage change: $13 \pm 46\%$) but not in the left ($7.7 \pm 39\%$). At six months, the isometric muscle strength of the knee extensors was not significantly different from baseline. Healthy volunteers increased knee extensor strength significantly in both legs after the intervention (right= $16 \pm 7\%$, left= $18 \pm 14\%$) indicating that the training intensity was adequate to produce strength changes.

Table 2-6 Changes in participation, mood and fatigue from baseline to 12 weeks in healthy and PN participants and from baseline to 6 months in PN group.

PN					Healthy			
Measure	Baseline	Change after exercise (n=14)	p	Change at 6 months (n=14)	p	Baseline	Change after exercise (n=8)	p
SF-36: Physical Function	70 (15-90) δ	10 (5 to 17.5)*	0.003	10 (2.5 to 17.5)*	0.02	95 (80 -100)	1.88 (-7.5 to 0)	ns
RLP	100 (0-100)	0 (-25 to 33)	ns	0 (-25 to 25)	ns	93.8 (50-100)	-6.3 (-50 to 0)	ns
RLM	100 (0-100)	12.5 (0 to 33)	ns	0 (0 to 25)	ns	100 (100-100)	-1.4 (-5.6 to 25)	ns
Social function	94.4 (55.5-100)	0 (-5 to 11.1)	ns	0 (-5.6 to 11.1)	ns	94.5 (66.7-100)	4.2 (-5.6 to 16.7)	ns
Mental health	82 (20-100)	4 (0 to 16)	ns	4 (0 to 14)	ns	79.5 (52-92)	4.5 (0 to 10)	ns
Energy and vitality	60 (15-95) †	12.5 (2.5 to 22.5)*	0.02	5 (5 to 15)	ns	73.8 (50-90)	3.1 (-5 to 10)	ns
Pain	72.8 (44.4-100) δ	11.1 (0 to 16.7)	ns	5.6 (0 to 16.7)	ns	91.7 (77.8-100)	-1.4 (-5.6 to 5.6)	ns
Health perception	53.5 (30-82)	12 (6 to 19)*	0.002	11 (0 to 18.5)	ns	76.8 (57-95)	-4.4 (-15 to 5)	ns
PCS	44.3 ±6.9 δ	5.8 (2.2 to 9.4)*	0.004	4.3 (1.5 to 7.4)*	0.01	56.9 (50.8-60.3)	-1.8 (-6.4 to 2.2)	ns
MCS	52.5 ±11	2.3 (-3.8 to 8.3)	ns	0.9 (-5.4 to 7.2)	ns	53.8 (40.6-59.3)	2.1 (-7.9 to 3.4)	ns
FSS	4.6 (1.5-6.11) †	-0.6 (-0.17 to -1.2)*	0.009	-0.6 (-0.2 to -1.45)*	0.01	3.3 (2.7-3.7)	-0.6 (-0.2 to -1.2)*	0.04
HADS Anxiety	6 (2-16)	-2 (-0.5 to -3.5)*	0.02	-2 (0 to -4.5)*	0.04	4 (0-9)	0.25 (-1.5 to 1)	ns
HADS Depression	1.5 (0-16)	-1 (-0.5 to -3)*	0.04	-0.5 (0 to -1.5)	ns	1 (0-7)	-0.13 (-1 to 1)	ns
BDI	3 (0-25)	-2.5 (0 to -6.5)*	0.04	-0.51 (-4.5 to 3)	ns	0 (0-12)	0.5 (-3.5 to 4)	ns

Baseline scores are all median (range) except for the SF-36 Physical Component Summary scores (PCS) and Mental Component Summary scores (MCS) which are mean ±SD. Changes after exercise and six months are all median (95% CI) except PCS and MCS which are mean (95% CI). A negative change indicates improvement on the FSS, HADS and BDI. A positive change indicates improvement from baseline for all other tools. RLP – role limitation physical, RLM – role limitation emotional. * indicates significant difference from baseline. † denotes significant difference between PN and healthy participants at baseline at p<0.05, **δ** at p<0.01.

Changes in cardiovascular fitness and walking

Peak heart rate, workload on exercise testing, PCI, mPCI and ten metre walk times, before and after the exercise intervention and at six month follow up are displayed in Table 2-7.

There were no significant changes in the performance of healthy volunteers on any of these outcomes. In PN participants, total work done during the exercise test increased significantly from baseline to after the intervention. Increases in peak workload produced on the exercise test approached significance in the PN group ($p=0.06$) but improvements in workload were not significantly different from baseline at six months.

Participants with PN had a significant reduction in their energy cost of walking measured by the mPCI, which was maintained at six months, although PCI and ten metre walk times were not significantly different from baseline at any point.

Statistical Power

Changes on the SF-36 PCS after exercise were used to calculate retrospective power as the primary outcome, the ODSS, was not parametric. The power of the study was 0.87 (two tailed $p=0.05$). This decreased to 0.64 at six months.

Table 2-7 Changes in cardiovascular parameters, knee extensor strength, activity levels and walking ability in PN and healthy participants

PN						Healthy		
Measure	Baseline	Change after exercise (n=14)	p	Change after 6 months (n=13)	p	Baseline	Change after exercise (n=8)	p
Right knee extensors (N)	304±138.7 (98-541)	38 (4 to 69)*	0.03	37 (-23 to 93)	ns	374.2 (242-511)	54 (35 to 73)*	<0.001
Left knee extensors (N)	297.4± 98.3 (97-517)	23 (-5 to 51)	ns	12.2 (-42 to 66)	ns	341.9 (194-439)	64 (19 to 110)*	0.01
Resting heart rate (beats min ⁻¹)	75±15 (57-88)	-6 (-12 to 1)	ns	-3 (-14 to 1)	ns	70±7.2 (55-79)	-2 (-6 to 1)	ns
Peak heart rate (beats min ⁻¹)	148±17.2 (133-181)	1 (-10 to 10)	ns	-4 (-22 to 13)	ns	165±9 (156-185)	-3 (-13 to 6)	ns
PCI (beats m ⁻¹)	0.35±0.14 (0.1-0.7)	-0.03 (-0.08 to 0.03)	ns	0.002 (-0.05 to 0.04)	ns	0.37±0.1(0.26-0.58)	0.008 (-0.35 to 0.05)	ns
mPCI (beats m ⁻¹)	1.66±0.6 (1.23-3.6)	-0.12 (-0.01 to -0.2)*	0.04	0.16 (0.6 to 0.26)*	0.01	1.3±0.32 (1-2)	-0.05 (-1.5 to 0.05)	ns
Fast 10 m walk test (s)	6.5±2.2 (4-12.6)†	0.4 (-0.4 to 0.53)	ns	-0.04 (-0.5 to 0.5)	ns	4.7±1 (3.6-6.4)	0.08 (-0.5 to 0.68)	ns
Preferred pace 10 m walk test (s)	9±2.5 (6.1-16)†	0.4 (-0.1 to 0.8)	ns	-0.05 (-0.5 to 0.6)	ns	6.7±0.1 (5.5-7.8)	0.025 (-0.5 to 0.5)	ns
Peak workload (Watts)	150±235 (60-300)	14 (0 to 28)*	0.06	7 (-6 to 20)	ns	188±53 (90-240)	11 (-7 to 30)	ns
Total workload (Watts)	375±306 (34-1350)	136 (13 to 137)*	0.03	4 (-96 to 104)	ns	627±302 (135-1000)	35 (-92 to 163)	ns

* indicates significant difference from baseline. All baseline values are means ±SD (range); change scores are mean change (95% CI). † denotes significant difference between PN and healthy participants at baseline at p<0.05, ‡ at p<0.01.

2.5.5. Properties of outcome tools

The floor and ceiling effects and responsiveness for outcome tools which demonstrated a significant difference after the intervention are presented in Table 2-8 (Page 90). The appropriateness, suitability and burden of tools are considered in greater depth in the discussion (Section 2.6.4, Page 98).

Primary outcome tool

Total ODSS scores had a floor (maximum limitations) or ceiling (no limitations) effect in 3 participants (3/14; 21%) which exceeds recommended values (<15%) (McHorney 1998). A ceiling effect on the lower limb section was apparent as six participants (6/14; 43%) scored zero on the lower limb section, indicating no activity limitations, despite reporting reduced physical functioning and difficulties with ambulation on other tools. This indicates that the ODSS may not be a suitable indicator of limitations affecting mobility. After exercise, the responsiveness of the ODSS was low (SRM: 0.34) but increased at six months (SRM: 1.4).

Secondary outcome tools

Over 15% of scores on the Beck depression inventory were at the floor of the scale in PN participants (McHorney 1998). The HADS had acceptable floor and ceiling effects (Table 2-8) but was observed to have some items that, whilst representing depression, could also correspond to limitations in physical functioning, reducing face validity.

Despite demonstrating a significant improvement after intervention, the FLP psychosocial component had a considerable ceiling effect (21%). Neither the HAQDI nor the physical component of the FLP demonstrated significant changes in physical functioning after the intervention despite other tools (SF-36) indicating significant improvements. The FLP also caused considerable respondent and administrator burden, taking approximately 25 minutes to complete and ten minutes to score.

The health perception and physical functioning subscale scores on the SF-36 with the HADS anxiety subscale demonstrated the largest responsiveness after exercise (all SRMs exceeded 0.6). These scales were also quick and easy to complete, but transformation of the SF-36 raw scores to subscale and component summary scores took approximately 15 minutes.

Table 2-8 Floor and ceiling effects and responsiveness for outcome tools that demonstrated a significant improvement after exercise in PN participants

Measure	Range of scores at baseline	No. at floor and ceiling (%)	Responsiveness after exercise	Responsiveness after six months	Overall mean responsiveness
ODSS	0 to 7	3 (21)	0.34	1.4	0.87
SF-36 Physical function	15 to 90	0	0.68	0.66	0.67
SF-36 Mental health	20 to 100	1 (7)	0.6	0.28	0.44
SF-36 Energy and vitality	15 to 95	0	0.59	0.25	0.42
SF-36 Health perception	30 to 82	0	1.59	0.78	1.19
Rotterdam Handicap Scale	25 to 36	2 (14)	0.6	0.6	0.6
HADS Anxiety	2 to 16	0	0.77	0.9	0.84
HADS Depression	0 to 16	1 (7)	0.17	0.3	0.24
Beck Depression inventory	0 to 25	3 (21)	0	0.3	0.15
Fatigue severity scale	1.56 to 6.11	0	0.5	0.38	0.44
PCS	33.6 to 54	0	0.51	0.67	0.54
FLP Psychosocial component	0 to 22	3 (21)	0.28	0.46	0.74

ODSS - Overall Disability Sum Score, HADS – Hospital Anxiety and depression questionnaire, PCS – physical component summary score from SF-36, MCS – Mental component summary score from SF-36, FLP – Functional limitations profile. Responsiveness calculated using distribution free formula (Page 77).

2.6. Discussion

This investigation was the first study to establish the practicality of a 12 week community based exercise intervention for people after GBS or with CIDP and to identify possible changes in impairments, activities and participation after the intervention, fulfilling the first aim of this thesis. The PN volunteers in this study complained of persistent impairments and chronic activity limitations which were refractory to curative medical treatment. For such individuals, self-management by regular exercise may be attractive if it could be shown to be practical and beneficial. Indeed, 41 people volunteered to participate in the trial and many more people contacted the investigator to convey their enthusiasm and support for the investigation, despite knowing they were not eligible for inclusion. Only two PN participants did not complete the programme, for reasons beyond their control (change in drug treatment and leaving the UK). Although based upon self report, which is liable to bias and inaccuracies in recall, adherence to the programme appeared good. Despite this flaw and other limitations in the design of the investigation, the response to the call for participants and the subsequent study findings suggest that many people with PN perceive exercise to make a valuable contribution to recovery and health maintenance.

The majority of healthy volunteers and people with PN reported successfully completing the exercise programme, and being able to exercise independently without sustaining injuries either at home or at a local gym. Significant improvements in activity limitations, experienced fatigue, anxiety and aspects of participation were apparent after the intervention in PN participants and were maintained at six months.

The findings of this study should be viewed with caution as there were several significant limitations in its design. These limitations are discussed in Section 2.6.5 but include the absence of a non-exercising PN control group, small sample and lack of rater blinding. Consequently, improvements in functioning seen after the intervention cannot confidently be attributed to the exercise intervention itself. Despite these limitations, the results indicate that a physiotherapist prescribed community based exercise intervention was practical for people with PN and these data support and inform further investigation of exercise in this patient group.

2.6.1. Practicality and adherence

All volunteers were able to exercise in an unsupervised community setting following clinical assessment and equipment provision by a physiotherapist. Many potential participants who contacted the investigator did not conform to the inclusion criteria of living within reasonable travelling time to the research site (13 from 41) and so could not be included. Therefore, achieving satisfactory recruitment and retention of willing participants for a future randomised controlled trial is likely to require a multi-centred national or international trial design.

Two participants in each group left the study for reasons which were not directly influenced by exercise. This was identical to the attrition reported from a supervised training intervention in

people with CIDP or after GBS (Garssen et al. 2004). No injuries or unwanted effects related to the programme that necessitated missing exercise sessions were reported, although this relied upon participants mentioning difficulties to the assessor. After initial instruction and provision of a booklet detailing their exercises, all participants reported that the programme was realistic and practical. However, this and the report of adherence, were likely to be biased by a desire to please the investigator which limits confidence in these findings. These effects could be ameliorated by using an independent rater in future work.

After completion of the exercise programme, PN participants reported improvements in energy, fitness and confidence to perform activities of daily living during an informal interview. Ten participants stated that they continued to exercise at six months, which may confer long term health benefits. The most commonly reported unwanted effects of the exercise programme were transient and mild muscle and joint ache, usually on the day after exercise, which did not limit usual activities or exercise. This suggests that the intervention was well tolerated. Although these findings would be fortified if detailed symptoms had been explicitly and more rigorously monitored, the presence of specific side effects of exercise were not sought overtly, as it was considered that this would influence the participant's report (Ruhland 1997). The side effects reported here are similar to those described by 18 people with CIDP or after GBS after completing 12 weeks of supervised aerobic training and in 14 participants with chronic PN after a combined training programme (Garssen et al. 2006a; Ruhland 1997).

Informal exit interviews also revealed that participants found the exercise equipment to be uncomplicated and the exercises straightforward to complete. There were no reported injuries linked to exercise and the positive comments from PN participants suggested that they found the intervention to be acceptable and practical. The competence of people with inflammatory PN to exercise in an unsupervised community setting has not been reported previously. However, over 40% (of 42) of people one year after GBS have not returned to their pre-morbid leisure activities, including sports, indicating that they struggle to recommence physical activities (Bernsen et al. 2002). Although no studies have identified reasons for reduced participation in physical activities in PN, several common causes for people with a range of disabilities have been identified. These include inadequate or unsuitable equipment, emotional and psychological barriers and a lack of knowledge by some fitness professionals (Rimmer et al. 2004). Indeed, some people with PN are likely to encounter difficulty when using conventional exercise equipment (e.g. a treadmill) due to impaired balance, reduced sensation and strength, resulting in exercise being perceived as difficult, unpleasant and potentially hazardous. This was exemplified in this study by one participant who could not use the standard exercise bike and who required specialised equipment.

Adherence was only able to be judged from participant report in exercise diaries as several PN and healthy participants struggled to consistently record their heart rate using the monitors during their exercise sessions. Consequently these data were unreliable and were not used. The difficulty in recording heart rate appeared to be because heart rate was displayed continuously and so participants forgot to press the record button. In addition, the stop

(recording) button was situated on the outer side of the watch and was often pressed accidentally. Some recordings from participants who exercised in a gym were also affected by interference from other machines. Although exercise diaries are a common method of reporting adherence in exercise studies, they introduce bias as self-report is affected by inaccurate recall, the desire to please the investigator and often results in over-estimation of exercise behaviours (Jakicic et al. 1998; Tudor-Locke and Myers 2001).

Although it is acknowledged that the accuracy of self report is limited, adherence in this study appeared good as the majority of participants reported completing the programme within the allocated time. These findings are similar to previous community based studies in neuromuscular disease (Agre et al. 1997; Kilmer et al. 1994; Wright et al. 1996) although factors affecting practicality were not reported in several (Aitkens et al. 1993; Chetlin et al. 2004; Lindeman et al. 1995; Pitetti et al. 1993).

Three PN participants and one healthy volunteer took longer to complete the 36 sessions than the recommended three month time period. Reasons for missing exercise sessions were often factors limiting opportunities to exercise including increased work demands, getting married and moving house. These issues are a common challenge to maintaining regular exercise for most people (Martin and Dubbert 1985) but this could indicate that the training frequency of the intervention was impractical for people with PN. However, these factors are more easily accommodated by an independent community based exercise programme as participants could choose when to exercise. Community based programmes have been shown to increase adherence (completed exercise sessions : 68%) in comparison to centre based exercise (36%) in older adults, supporting the design of the programme used in the current study (Ashworth et al. 2005).

The continuation of regular exercise is vital to gain sustained health benefits and so the maintenance of exercise could be used as a measure of the success of an intervention to promote good health (Dishman 1990). In the current study, six months after completing the programme, ten PN participants (from 14) reported maintaining aerobic, strengthening and/or functional exercises at a similar intensity and duration to the prescribed programme. This continuance of exercise suggests that the majority of PN participants considered the intervention to be worth continuing and that the components of the original programme were acceptable and practical. This result is also supported by the study by Garssen et al. (2005) in which ten from 18 PN participants reported continuance of exercise two years after a 12 week supervised exercise programme.

2.6.2. Baseline stability

Two baseline measurements, taken one month apart before beginning the exercise programme, familiarised volunteers with testing procedures and provided data to evaluate the stability of their condition. This duration was chosen after consultation with the GBS support group as the steering committee anticipated that a pre intervention period of 12 weeks may deter potential volunteers from participation, reducing recruitment. However, it is recognised that one month was too short to act as a pre-intervention control period.

All PN participants were screened by a neurologist to ensure their neuropathy was stable. Despite this, in the PN group, there was a significant improvement between baselines on one subscale of the SF-36 questionnaire (role limitation physical, RLP) with two PN participants demonstrating large increases in their scores (increasing by 75 and 100 points) at the second baseline measurement. A true change in neurological stability is unlikely as neither reported any significant change in health status on questioning or on any other outcome tools. The apparent improvement on the RLP subscale scores could be caused by a learning effect as the overall variance of scores was somewhat decreased on the second measurement, indicating familiarisation (Bouchet et al. 1996). Participants may have altered their answers on the second measurement session due to the Hawthorne effect as, by being involved in research, they were the focus of special attention (Bouchet et al. 1996). This effect has been shown to produce significant changes in scores on the SF-36 questionnaire in healthy people, including in the RLP subscale (Bouchet et al. 1996).

Healthy volunteers did not demonstrate significant differences on the SF-36 questionnaire between baseline measurements in this study but significant improvements in fatigue and the time taken to walk ten metres were evident at the second baseline. This may also be attributed to the Hawthorne and learning effects.

In future studies, the impact of these effects on the results could be minimised or eliminated by greater participant familiarisation with the outcome measures and the inclusion of a non exercising control group.

2.6.3. Overall changes in outcomes after the exercise intervention

The results demonstrate that there was a significant reduction in activity limitations experienced by people with PN following the exercise intervention. However, limitations in the design of the study meant that there was risk of selection, measurement and exposure bias and the lack of a PN control group meant that changes after the intervention could not be attributed to the exercise programme.

Activity limitations

The primary outcome tool, the ODSS, demonstrated a median improvement of 0.5 after the intervention and the upper and lower limb ODSS subscale scores also demonstrated significant improvements. The total ODSS score remained significantly improved from baseline at six months (median change: 1, range: -3 to 1), but subscale scores did not.

An overall change of 0.5 on a very similar scale to the ODSS (GBS disability scale) has been proposed as worthwhile to PN patients, suggesting the improvement seen in this study is clinically meaningful (Hughes et al. 2001).

A ceiling effect was apparent on the total ODSS as three from 14 scores (21%) were at the ceiling of the scale. Six from 14 scores (43%) were at the ceiling of the lower limb subscale which indicates that further important changes in functioning were not effectively demonstrated. This limitation, and the properties of other outcome tools, is discussed further in Section 2.6.4 (Page 98).

Participation and EADL

Participants with PN reported large, significant improvements in physical function (PF) and physical component summary (PCS) scores on the SF-36 (PF: mean change; 95% CI: 10, 5 to 17.5; PCS: 5.8; 2.2 to 9.4). This is an important finding as it meant that PCS scores were within healthy population derived values after the intervention (Ware and Kosinski 2003) and these changes were maintained at six months. Garssen et al. (2004) reported similar improvements in PCS scores after a supervised aerobic exercise intervention in 20 people with CIDP or after GBS, although in Garssen et al.'s work (2005a), these changes were not maintained at follow-up despite reports of continuing exercise. This may have resulted from the longer (two year) follow-up period used (Garssen et al. 2005a). Alternatively, the maintained improvement in the current study may be due to inclusion of combination of strength, aerobic and functional training, or to improved coping and symptom control which is produced by community based exercise (Alderson et al. 1999).

A significant improvement in the total FLP score indicated that PN participants perceived fewer restrictions after the intervention (FLP mean change, 95% CI: -4.9, -0.8 to -8.15). Surprisingly, this significant improvement occurred despite no significant change on the physical subscale of the FLP. There were also no significant improvements in scores on the HAQDI, a measure of EADL. This was also initially surprising as several other tools which measured physical function and participation demonstrated significant improvements. However, at baseline several PN participants were at the ceiling of HAQDI (n=6) and FLP physical subscale (n=3), indicating maximal functioning, so scores could not reflect further improvement. These findings indicate that these tools are not appropriate to capture participation in PN.

Experienced fatigue and mood

Experienced fatigue is a common, persistent symptom and contributes to reduced activity in inflammatory PN (Lennon et al. 1993; Merkies et al. 1999). After the intervention, the PN group demonstrated a significantly reduced severity of fatigue measured on the FSS (FSS mean change, 95% CI: H: -0.6, -0.2 to -1.2; PN: -0.6, -0.17 to -1.2) and these improvements were maintained at six months. Healthy participants also reported significantly reduced fatigue after the intervention but as fatigue was also significantly reduced between baseline measurements in this group, the significance of this findings is unclear (FSS mean change, 95%: -0.6, -0.2 to -1.2). There was also a significant increase in energy and vitality measured on the SF-36 in the PN group (mean change, 95% CI: 12.5, 2.5 to 22.5). Similar findings have been reported in 18 volunteers after GBS and with CIDP who completed a 12 week exercise programme although fatigue scores demonstrated a larger improvement than those seen here (mean decrease of FSS scores: 1.3, SD: 1.9) (Garssen et al. 2004; Garssen et al. 2005a). This is likely to be because participants in their study were specifically selected to have severe fatigue (FSS scores greater than 5). The reduction in experienced fatigue after the intervention cannot be attributed to exercise as neither Garssen et al. (2004) nor the current study included a non-exercising control group. However, these findings suggest that factors which were improved by an exercise intervention could be associated with the severity of fatigue. Future work to

investigate these factors could provide a mechanism for understanding and managing experienced fatigue in people with PN and is presented in Chapters Five and Six.

There was a significant improvement in anxiety scores on the HADS after the intervention (mean change, 95% CI: -2, -0.5 to -3.5) which was maintained at six months. Anxiety has been reported to adversely affect activities and quality of life in people with PN (Lennon et al. 1993). After the intervention, several PN participants also commented that they felt less nervous when performing physical activities of daily living. Although a reduction in anxiety could be attributed to improved confidence after contact with the investigator, it is possible that the exercise intervention improved physical functioning and mental health via psychological and biological interactions (Weyerer and Kupfer 1994).

Average depression scores on the BDI and HADS were also reduced after the intervention (mean change, 95% CI; HADS: -1, -0.5 to -3; BDI: -2.5, 0 to -6.5), but were not significantly different from baseline at six months. This finding is supported by other studies in PN (Garssen et al. 2004; Garssen et al. 2005a), but has little significance as the majority of participants had scores that fell within normal limits.

Muscle strength, walking and cardiovascular fitness

There were modest, significant improvements in the strength of the knee extensors after the intervention (+13%) in the PN group, which were trained by all volunteers, but these changes were not sustained at six months. The increase in strength in healthy participants was also significant (+16%), indicating the training stimulus was appropriate to elicit changes in muscle performance. Importantly, the results of this study show no evidence over-work weakness in the PN group, suggesting that unsupervised isometric strength training was practical and not detrimental.

These findings are similar to reported increases in strength, ranging from 7% to 60%, after targeted training in people with neuromuscular diseases, including PN (Agre et al. 1997; Aitkens et al. 1993; Chetlin et al. 2004; Garssen et al. 2004; Lindeman et al. 1995; Milner-Brown and Miller 1988). In a study in inflammatory PN, Garssen et al. (2005b) reported that strength remained improved up to two years after exercise training, unlike results at six months in the current study. This may be explained by the isokinetic strength training that they used, which may be more closely related to functional muscle performance than the isometric training used here. Isometric contractions were selected for testing in the current study as they were used during training and the use of the same muscle action to that used in training is reported to demonstrate the greatest strength changes when testing (Khouw and Herbert 1998; McGlynn 1972). Muscles were trained isometrically for reasons of safety as it was anticipated that people with PN who had reduced proprioception and muscle weakness risked injury performing unsupervised dynamic strengthening exercises.

Some reports suggest that impairments in muscle strength and endurance cause activity limitations for people with inflammatory PN (Merkies et al. 2003b) whilst others have argued that these physical impairments have only a weak contribution to performance (Bussmann et

al. 2007). In this study, the maintenance of improved activity limitations at six months despite strength returning to near baseline levels suggest that strength may have little impact on perceived activity limitations. Similarly, times to complete the ten metre walk tests did not change significantly after the intervention or at six months despite alterations in reported walking ability on the ODSS and items on the SF-36. This indicates that the speed of walking measured over short distances, as in these tests, does not greatly influence daily activities in PN participants and that other tools to assess mobility are required.

However, there were significant improvements on the mPCI that were sustained at six months (mean change, 95% CI: -0.12, -0.01 to -0.2). This indicates that the aspects measured by the mPCI and which influence walking efficiency were changed after the intervention. Wide variability on scores on the PCI meant that this measure showed no significant improvement.

Participants with PN produced a significantly greater total workload during exercise testing (mean increase=+36%) after the intervention than before. They could cycle for longer and this suggests improved aerobic endurance. However, alterations in total workload after training in healthy volunteers were much smaller and did not reach significance (mean increase=+6%). Changes in peak workload during exercise testing after the intervention were small in the healthy group, but improvements approached significance in PN participants (+9%, $p=0.06$). Other reports have described much larger increases in peak workload (+29%) after supervised aerobic training in people with PN (Garssen et al. 2004; Pitetti et al. 1993). This could imply that the aerobic training stimulus in the current study was insufficient to produce tangible changes in cardiovascular fitness.

However, on closer scrutiny, there was a wide variance in peak and total workload values from exercise testing. This was most marked in the healthy group but was also apparent in PN participants. This indicated that some individuals improved whilst others did not change from baseline, suggesting that they did not adhere to the aerobic training component of the programme. Better monitoring of the aerobic component of the programme would have provided more objective data on training intensity and adherence, but this was not possible due to problems with the heart rate monitoring equipment (discussed in Section 2.6.1). If more robust and reliable equipment could be used in future studies, it would allow these data to be collected whilst still facilitating participants to exercise independently in the community.

It is also likely that, as many participants trained by walking or running and not using a cycle, improvements in training specific aerobic fitness were not apparent on cycle ergometer testing. This is a limitation of cycle based exercise testing as participant's performance may be influenced by factors other than aerobic function such as leg strength and coordination (American College of Sports Medicine 1995) but cycle based exercise testing was used in this study as many people with PN have difficulties with balance. In future, estimation of aerobic fitness could be measured directly during a participant's preferred training activity using calorimetry or a more functional exercise test protocol. Participants could also be restricted to one aerobic training modality as others have done (Garssen et al., 2004).

2.6.4. Properties of outcome tools

Primary outcome tool - The Overall Disability Sum Score

The ODSS was quick and straightforward to complete and appeared to capture aspects of functioning that were relevant to people with PN. It demonstrated a ceiling effect at baseline as three from 13 (21%) participants scored zero, indicating no activity limitations (McHorney 1998). On the lower limb section, six from 13 PN participants (46%) scored zero, despite indicating limitations in mobility on other questionnaires. The omission of items which measure more minor limitations in mobility, such as running, suggests that the ODSS is not sufficiently sensitive to measure the presence of, and alterations in, these limitations which may still be of great importance to participants. Further work is therefore necessary to evaluate other tools in PN or to reduce the ceiling effect of the ODSS whilst maintaining its other properties; a new version of the ODSS, the Overall Neuropathy Limitations Scale, ONLS, is considered in Chapter Three.

Secondary outcome tools

Of the secondary outcome tools assessed, the SF-36 questionnaire physical function, health perception subscales and PCS subscales and the HADS anxiety scale were most responsive after exercise (Table 2-8), and had floor and ceiling effects within published recommendations (McHorney 1998).

Whilst the HADS anxiety had good face validity, one item on the HADS depression scale could be confused with physical limitations ("I feel slowed down all the time..."). This may account for the small but significant improvement seen on the HADS depression scale after the intervention (mean change, 95% CI: -1, -0.5 to -3), despite no significant changes in depression measured by the BDI. As average depression scores were within normal limits, these findings indicate that depression is not an important outcome in a future trial of exercise in PN but, if it is to be measured, other tools which do not contain physical items should be considered.

The FSS had little burden and reflected moderate to severe levels of experienced fatigue in PN participants, indicating it is a useful tool in this patient group and supporting the findings of others (Merkies et al. 1999). Although the FSS reflected significant alterations in experienced fatigue after the intervention, it was only moderately responsive (overall responsiveness= 0.4) which suggests that other fatigue tools could be considered in future work.

The RHS demonstrated face validity, acceptable floor and ceiling effects, was moderately responsive to changes after the intervention (overall responsiveness= 0.6) and had little burden. This suggests that the RHS and SF-36 (discussed above) are suitable and appropriate in PN.

Several tools did not appear appropriate for use in this type of intervention in PN. Scores on the HAQDI were unchanged after the intervention despite similar tools measuring significant improvements (for example, aspects of the SF-36 and FLP). It is possible that the specific

aspects of EADL measured by the HAQDI were unchanged or that the HAQDI was insensitive to change in people with PN after the exercise intervention. This suggests that another EADL tool should be investigated for future use.

Although the total FLP scores demonstrated significant improvements after the intervention (Table 2-5), the physical subscale did not, despite other tools reflecting significant activity limitations. The FLP also produced a considerable burden as it took up to 25 minutes to complete. Taken together, these limitations deter from its use in future studies.

The ten metre walk tests (preferred pace and as fast as possible) were not responsive to change after the intervention, despite significant improvements in self reported walking ability on other tools. Although this highlights the difference between self report and objective measurement, it suggests that walking speed did not reflect wider mobility in PN participants. The mPCI demonstrated significant improvements after the intervention and so it may be an appropriate tool to measure walking ability for people with PN. However, its validity and reliability must be investigated before it can be considered for use. This investigation and other studies of outcome tools to indicate walking ability is described in Chapter Four.

Based on the findings from this investigation, recommendations of outcome tools for use in future studies of exercise in PN are presented in Table 2-9.

Table 2-9 Recommended outcome tools based on their performance in this study

Recommended	Not recommended
SF-36 subscales - <ul style="list-style-type: none"> Physical Function Health perception Physical Component Summary 	Beck Depression Inventory
Rotterdam Handicap Scale	Health assessment questionnaire disability index
Hospital Anxiety and Depression Scale	Functional limitations profile
Fatigue Severity Scale	10 metre walk tests
Modified Physiological Cost Index [#]	
[#] requires investigation of reliability and validity (Chapter Four)	

2.6.5. Limitations of this study and implications for future work

In addition to the limitations already discussed, there were a number of limitations which are considered in greater depth here.

Absence of a PN control group

The prospective cohort study design was chosen to fulfil the first aim of the study by establishing the practicality of exercise for PN and factors affecting recruitment to a RCT. Both GBS and CIDP are rare (Hughes and Rees 1997; Lunn et al. 1999) and finding volunteers with stable disease, no disqualifying medical conditions and who could travel to London was difficult. A non-exercising control group was not included as it was anticipated that the relative scarcity of people with PN who could attend for testing and met the inclusion criteria would prevent recruitment of sufficient participants within a reasonable timescale. This concern was justified in part, as although many people contacted the investigator, only 40% were eligible to participate. Furthermore, randomisation to a non-exercising control group is likely to have been unacceptable for some volunteers, which would have increased withdrawal from an already limited target population. Steps were taken to strengthen the design, despite the absence of a control group. The possibility of spontaneous recovery was minimised by selecting participants with clinically stable PN and including a short pre-intervention baseline period. Nonetheless, the inclusion of a control group undertaking a non-exercise based intervention would have allowed observation of the extent to which spontaneous recovery and other uncontrolled factors contributed to the results.

However, it is recognised that complex interventions are difficult to control as several factors including contact with a medical professional, desire to please the investigator and expectations of improvement by study volunteers influence self report and performance adequately (Hawe et al. 2004). Whilst the placebo effect is often beneficial (Bouchet et al. 1996), the use of realistic placebo groups in exercise interventions is difficult, not least because the benefits of exercise are widely documented and participants expect improvement (O'Halloran et al. 2002). It is also difficult to blind participants to a participatory investigation such as exercise and blinding does not reflect the usual clinical situation. In order to provide a true control for the current study, a non-exercising PN group should have undertaken an ethical placebo intervention which provided comparable contact with the investigator and elicited similar expectations of improvement as an exercise intervention. A controlled intervention of this nature does not exist. Others have used relaxation or cognitive behavioural therapy as a control in other patient groups (Bateman et al. 2001; Ridsdale et al. 2004) but they do not elicit similar participant expectations to exercise. The range and duration of symptoms demonstrated by PN participants in this study also indicate that it may not be possible to match control and intervention groups, limiting the usefulness of group comparison. A delayed intervention control group would have strengthened the design but was not included as the time for recruitment was not known before commencing this study. Although this would

not exclude some limitations, such as patient expectations and lack of participant blinding, it would have provided some certainty that improvements were not due to spontaneous recovery.

Restricted sample

The results of this study are based upon a small number of self-selected PN participants which reduced the validity of the results. As inflammatory PN is relatively rare, a larger target population could be accessed by utilising a multi-centre trial design in future work but would require rigorous standardisation of testing procedures to ensure parity between centres.

A large trial of this nature may also aid recruitment of sufficient participants to allow diagnostic sub-group analysis. Although people with CIDP report many similar problems to those with GBS, it may not be legitimate to group these conditions together. Visual inspection of the data revealed little difference in outcomes between conditions in the current study, but analysis of sub-groups was not possible due to the small sample.

Nature of the data

Whilst participants completed a battery of outcome tools, very little qualitative data were collected. This meant the participant's perceptions of the intervention and the factors which were of importance to them could not be determined. In particular, this limited the understanding of reasons affecting adherence to the programme, potential changes in health behaviours and their beliefs about exercise. This could be remedied in future work by adopting a mixed methods approach and using qualitative techniques, such as interviews, alongside quantitative measurement.

Absence of blinding

The expectations of the assessor in this study are likely to have biased results. Recollection of previous performance by the assessor would predominantly affect impairment measurements which they recorded. Their expectations may also bias tools administered by interview such as the RHS and ODSS. The likelihood of the assessor recollecting previous results was limited as much as possible by ensuring all data were entered within 24 hours of assessment, and not examined prior to the next assessment visit (at least one month later). Standardised protocols and instructions were adhered to throughout to minimise the likelihood that the assessor could influence performance by providing different encouragement. Many other outcome tools were questionnaires completed independently by the participant, so are unlikely to be affected by assessor bias, but a future study should utilise a blinded assessor to eliminate this source of bias. However, participants were not able to be blinded, thus their expectations of improvement and effort is likely to have unavoidably influenced results.

2.7. Conclusions

The aim of this study was to investigate the practicality of a 12 week community based unsupervised exercise programme and its potential effect upon activity limitation and wider health in people after GBS or with stable CIDP. The results showed that an individually tailored combined exercise programme was practical and well tolerated in people with inflammatory PN and that they could exercise safely, without supervision, in their local community.

Following the intervention, PN participants had significantly improved physical functioning and decreased activity limitations. Other persistent symptoms, including fatigue and anxiety, which contribute to persistent disablement, were also significantly reduced. Many significant improvements were maintained at six months and the majority of PN volunteers reported continuing to exercise. Whilst this is based on self report, it suggests that the intervention produced important changes in health behaviour that could potentially reduce risks of secondary health problems in this patient group (McDonald 2002).

There were several limitations of this study including the absence of a non-exercising control group and lack of blinding. Consequently, the changes observed could not be attributed to the effect of the exercise intervention. The sample was also small reducing its external validity and preventing sub-group analysis. Despite its limitations, this study offers evidence to support the use of exercise in people with inflammatory PN but, perhaps more importantly, provides data to inform the design of a larger controlled trial.

Chapter 3. A new measure of activities for people with peripheral neuropathy – the overall neuropathy limitations scale

3.1. Summary

In this Chapter, the modification and evaluation of a disease specific measure of activity limitation for people with peripheral neuropathies (PN) is presented. The modified scale, the Overall Neuropathy Limitations Scale (ONLS), was derived from an existing scale, the Overall Disability Sum Score (ODSS), to overcome the ceiling effect that was apparent on the lower limb subscale when the ODSS was utilised in the exercise intervention study in Chapter Two.

The validity and reliability of the ONLS were examined in 100 participants (49 females, mean age (SD): 58 (15.1), with a wider range of PN than originally investigated for the ODSS (CIDP=41, PDN=15, GBS=12, CIAP=12, Other neuropathies=20). Its responsiveness was measured using 24 measurements from 19 participants over one year. The reliability and validity of the ONLS as an observed measure was also evaluated using four raters (two neurologists, two physiotherapists) in 35 participants.

The ONLS and ODSS demonstrated similar inter-rater reliability (ICC: 0.97). There were fewer scores at the ceiling of the ONLS lower limb subscale (n=8) than on the ODSS (n=13), indicating that the changes made to produce the ONLS had reduced a potential ceiling effect. Both the ONLS and ODSS had concurrent validity as they were significantly and moderately associated with the SF-36 and Rotterdam Handicap Scale (RHS) (both $r > 0.6$, $p < 0.05$). The ONLS was more closely associated with scores on a 12 item mobility questionnaire (Walk-12) than the ODSS, suggesting it was more able to measure mobility problems (ONLS: $r = 0.65$, ODSS: $r = 0.43$, both $p < 0.05$). However, the ONLS demonstrated somewhat lower responsiveness than the ODSS (ONLS: Standardised Response Mean (SRM), 95% confidence limits = 0.76, 0.67 to 0.81; ODSS: SRM = 0.88, 0.88 to 0.95). Whilst there were not significant changes in activity limitations between repeated measurements according to either scale and the sample was small, the reduced responsiveness of the ONLS was probably due to the two activities added to the lower limb section.

The ONLS demonstrated greater face validity, had fewer scores at the ceiling of the scale and was more able to reflect mobility problems for participants with PN, but it was somewhat less responsive than the ODSS. Further work should re-examine the responsiveness of the ONLS in a larger sample of participants undergoing larger changes in clinical status. However, future work could also develop new measures of activity limitations and/or evaluate other activity limitation tools for use in PN to overcome the shortcomings of the ODSS and ONLS.

This study has been published and is appended to this thesis:

Graham RC, Hughes RA. A modified peripheral neuropathy scale: the Overall Neuropathy Limitations Scale. *J Neurol Neurosurg Psychiatry*. 2006 Aug;77(8):973-7.

3.2. Background

Outcome tools which measure common, daily difficulties are necessary to evaluate status, guide treatment and determine rehabilitation goals (Chiou and Burnett 1985; Hobart et al. 1996). Alterations in activity limitations reflect changes which are of importance to the individual, and are thus considered to be most appropriate to describe the effects of rehabilitative interventions, including exercise (Wade 2003). However, few outcome measures commonly used in PN assess activity limitations, despite only 40% or less of the variance in functional status being explained by alterations in more frequently measured aspects of functioning such as strength and sensation (Molenaar et al. 1995; Molenaar et al. 1999).

There are a number of outcome tools which may be appropriate to indicate activity limitations in people with PN. However, several are not suitable as they do not capture the range of common activity limitations experienced in PN, have some redundant items and are likely to demonstrate a ceiling effect. One tool, the overall disability sum score (ODSS) was specifically designed to assess activity limitations in people with inflammatory PN (Merkies et al. 2002a). It was reported to be valid and reliable and was used as the primary outcome of activities in Chapter Two (Merkies et al. 2002a). The ODSS was originally derived from a scale which assessed activity limitations in multiple sclerosis, the Guy's neurological disability scale (Sharrack and Hughes 1999). It consists of a checklist for interviewing people, with a focus upon upper and lower limb functions (presented in Chapter One, Pages 51 to 53). Upper limb activities are scored from a maximum of five, and lower limb from a maximum of seven, which can be summed to produce a total ODSS score out of 12. A maximum overall score of 12, and subsection scores of five or seven indicate an inability to produce purposeful movement in both the upper and lower limbs and the upper or lower limbs respectively. Zero indicates no activity limitations in everyday activities.

The published properties of the ODSS were critically discussed in Chapter One (Page 51). Scores on the ODSS showed a significant improvement after the exercise intervention in Chapter Two. However, the ODSS demonstrated a ceiling effect at baseline in Chapter Two as three participants (from 14; 21%) scored zero, indicating no activity limitations, despite reporting problems on similar outcome tools. Scores on several tools such as the physical function (PF) subscale of the SF-36 questionnaire (median score at baseline: 85, range: 85-90) significantly improved after the intervention whereas scores on the ODSS remained at zero and thus the ODSS was unable to measure small but potentially significant improvements. These findings suggest that the ODSS might not be appropriate to measure changes after interventions in more able people with inflammatory PN.

On closer examination, the ceiling effect observed on the ODSS in Chapter Two appeared attributable to scores on the lower limb subscale. The ODSS does not fully represent lower limb limitations as it does not examine limitations such as difficulties in climbing stairs or running. One year after GBS, 18% (from 79) to 24% (from 42) of people were unable to run (Forsberg et al. 2004; Rees et al. 1998) and, in a small survey of 12 people with CIDP, ten

stated they struggled to climb stairs (Erdmann et al. 2005). However, rehabilitation, including exercise interventions, may improve these activities (Aitkens et al. 1993; Garssen et al. 2004; Lindeman et al. 1995) and so tools to capture these data are required. Furthermore, the properties of the ODSS have only been examined in GBS, CIDP and PDN which limits its clinical usefulness for other forms of PN.

As the ODSS has demonstrated reliability, responsiveness and concurrent validity in people with GBS, CIDP and PDN (Merkies et al. 2002a; Merkies et al. 2003a) and has been used to assess activity limitations in clinical trials and investigations (Hughes et al. 2004; Merkies et al. 2003a), it was anticipated that the modification of the ODSS could address the ceiling effect whilst maintaining its other properties. Therefore, the ODSS was modified to capture difficulties with running and climbing stairs with an aim to reduce the ceiling effect seen in Chapter Two. This new scale was called the Overall Neuropathy Limitations Scale (ONLS) and is shown on Page 107. The ODSS item “Does the patient have difficulty walking?” has been altered to “Does the patient have difficulty running, walking or climbing stairs?” on the ONLS. Therefore to score zero on the lower limb section of the ONLS, indicating no activity limitations, the respondent must report no difficulty running or climbing stairs, in addition to no difficulty walking.

An observed version of the ONLS, scored by clinicians watching participants perform the tasks outlined on the ONLS, was also designed for use in people with language or communication difficulties.

3.3. Aim

The aim of this study was to investigate the reliability, validity and responsiveness of the new ONLS outcome tool when used as a questionnaire with, and from observation in, people with PN.

3.3.1. Overall Neuropathy Limitations Scale (ONLS)

Overall Neuropathy Limitations Scale (ONLS)

Instructions : The examiner should question **and** observe the patient in order to determine the answers to the following Questions. .Note should be made of any other disorder other than peripheral neuropathy which limits function at the foot of the page.

ARM SCALE

Does the patient have any symptoms in their hands or arms e.g. tingling, numbness or weakness?

Yes ☐ No ☐ (if "no", please go to "legs" section)

Is the patient affected in their ability to:	Not affected	Affected but not prevented	Prevented
Wash and brush their hair	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Turn a key in a lock	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Use a knife and fork together (or spoon, if knife and fork not used)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do or undo buttons or zips	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dress the upper part of their body excluding buttons or zips	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If all these functions are prevented can the patient make purposeful movements with their hands or arms? Yes ☐ No ☐ Not applicable ☐

Arm Grade

0 = Normal

1= Minor symptoms in one or both arms but not affecting any of the functions listed **SCORE=_____**

2= Disability in one or both arms affecting but not preventing any of the functions listed

3= Disability in one or both arms preventing at least one but not all functions listed

4= Disability in both arms preventing all functions listed but purposeful movement still possible

5= Disability in both arms preventing all purposeful movements

LEG SCALE

	Yes	No	Not Applicable
Does the patient have difficulty running or climbing stairs?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Does the patient have difficulty with walking?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Does their gait look abnormal?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
How do they mobilise for about 10 metres (i.e. 33 feet)?			
Without aid	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
With one stick or crutch or holding to someone's arm	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
With two sticks or crutches or one stick or crutch holding onto someone's arm or frame	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
With a wheelchair	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
If they use a wheelchair, can they stand and walk 1 metre with the help of one person? <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If they cannot walk as above are they able to make some purposeful movements of their legs e.g. reposition legs in bed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Does the patient use ankle-foot orthoses/braces ?(please circle)	<input type="checkbox"/>	<input type="checkbox"/>	
If yes: (please circle) right/left			

Leg grade

0= Walking/climbing stairs/running not affected

1= Walking/climbing stairs/running is affected, but gait does not look abnormal **SCORE=_____**

2= Walks independently but gait looks abnormal

3= Requires unilateral support to walk 10 metres (stick, single crutch, one arm)

4= Requires bilateral support to walk 10 metres (sticks, crutches, crutch and arm, frame)

5= Requires wheelchair to travel 10 metres but able to stand and walk 1 metre with the help of one person

6= Restricted to wheelchair, unable to stand and walk 1 metre with the help of one person, but able to make some purposeful leg movements

7= Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs

Overall Neuropathy Limitation Scale = arm scale (range 0-5) + leg scale (range 0-7);

[range: 0 (no disability) to 12 (maximum disability)]

TOTAL SCORE=_____

Is there any disorder, other than peripheral neuropathy, which affects the above functions Yes ☐ No ☐

If **yes** please describe :

3.4. Method

3.4.1. Design and participants

A cross sectional design was used to investigate reliability and validity of the ONLS (Sim and Wright 2000). Participants with any form of PN were recruited from the Peripheral Nerve clinic and inpatient neurology ward at Guy's and King's College Hospitals, London. With permission from the local ethics committee and after informed consent was given, 35 people were filmed performing the tasks involved on the ONLS in addition to completing the ONLS, ODSS and several other questionnaires (detailed below).

With audit committee approval, the ONLS questionnaire was then audited in 65 more people attending the Peripheral Nerve clinic at Guy's Hospital. The ONLS interview was administered and scored according to the instructions in Appendix Three.

Sample Size

The estimate of the sample needed to investigate the properties of the ONLS was informed by Merkies et al. (2002b) who recruited 113 participants when initially evaluating the ODSS.

Face validity

Sixteen neurologists were shown the ODSS and ONLS and asked to anonymously complete a short questionnaire. They were asked which questionnaire they preferred (ODSS or ONLS), if they would be interested in using the ONLS in clinical practice and how well they considered the ONLS captured common problems in people with PN (very well, well, not very well, not at all).

Concurrent validity

The ODSS, ONLS interview and observed measures were administered by a physiotherapist (the author) or consultant neurologist (Professor R.A.C. Hughes). All questionnaires were completed in random order.

Scores on the ONLS interview and the observed version were compared to several other self report tools. These were the ODSS, SF-36 questionnaire, the Rotterdam handicap scale (discussed in Chapter One) and the Walk-12 (described and evaluated in Chapter Four) to investigate concurrent validity (Hamilton 1991; Hobart et al. 2003; Merkies et al. 2002b; Merkies et al. 2002c). Associations between scores on the ONLS, ODSS and these tools were examined separately in people with GBS, CIDP and other PN, to identify if either outcome tool remained similarly valid in wider forms of PN.

Measurements from routine clinical assessment were also collected. These comprised the time taken to walk ten metres as fast as safely possible (described in Chapter One, Page 55) (van Loo et al. 2003) and the isometric strength of the following pairs of muscles graded from a maximum of 70 by an expert neurologist (Professor R.A.C. Hughes) using the Medical Research Council (MRC, Page 45) sum score (Kleyweg et al. 1991; Medical Research Council

1976): shoulder abductors, elbow flexors, wrist extensors, first dorsal interossei, hip flexors, knee extensors and ankle dorsiflexors.

3.4.2. Hypotheses

It was hypothesised that:

H₁: ONLS scores would demonstrate significant and strong associations with the ODSS and physical function subscale on the SF-36,

H₂: ONLS or ODSS scores would not correlate strongly with the mental health and role limitation due to emotional problems subscales on the SF-36 questionnaire,

H₃: ONLS scores would demonstrate significant and strong associations with the Walk-12 and ODSS scores would not, as the ONLS is more sensitive to lower limb limitations

Null hypothesis (H₀): there would be no significant association between the ONLS, ODSS or SF-36 and, that associations between the ONLS and Walk-12 would be similar to those between the ODSS and Walk-12.

and

H₄: scores from the ONLS administered as an observed measure, would correlate less strongly with data collection tools based upon participant report, compared to scores from the ONLS applied as a questionnaire.

Null hypothesis(H₀): scores from the ONLS administered as an observed measure would demonstrate similar correlations with data collection tools based upon participant report, to scores from the ONLS applied as a questionnaire.

Correlation coefficients were judged to be small/low (0.1-0.3), moderate (0.3-0.6) or large/strong (>0.6) according to published criteria (Cohen 1977).

3.4.3. Reliability

Inter-rater reliability

In 20 participants, two raters completed the ONLS interview on the same occasion.

Film footage of 35 people performing the tasks on the ONLS was scored independently by four raters, two consultant neurologists (Professor R.A.C. Hughes, Dr Paul Holmes) and two senior physiotherapists (Dr Claire White and the author).

Intra-rater reliability

Video footage of ten people performing the activities described on the ONLS was re-scored by one rater (the author) three months after the first assessment.

3.4.4. Responsiveness

A longitudinal design was utilised to assess responsiveness (Sim and Wright 2000). Repeated measurements of the ONLS interview and ODSS were collected over one year from 19 participants. Five participants were re-assessed on a third occasion, producing 24 repeated

ODSS and ONLS scores. Seventeen participants also rated their abilities relative to their previous assessment on a global rating scale (worse, same, better). These participants (n=17) were re-filmed and scored by one rater (the author) to determine the responsiveness of the ONLS as an observed measure. It was anticipated that all participants would undergo some change in their status over this time as they attended hospital for follow up and treatment.

3.4.5. Analysis

The distribution of scores on the ONLS and ODSS was examined to determine floor and ceiling effects. Differences between scores from the ONLS interview, ODSS and observation of the tasks outlined on the ONLS were examined using the Friedman (non parametric repeated measures) test.

Associations between age and gender with ONLS and ODSS scores were investigated by examining scatter plots and calculating Spearman's rank correlation coefficients.

Validity

Responses from neurologists were examined to judge the face validity of the ONLS.

Concurrent validity was investigated with Spearman's rank correlation coefficients between the ONLS, observed ONLS and the ODSS scores, and subscales on the SF-36, the MRC sum score, Walk-12 questionnaire, Rotterdam handicap scale and ten metre walk time. These were repeated for two diagnostic subgroups, people with GBS and CIDP and those with other forms of PN. Correlation coefficients were compared to test the hypotheses listed on Page 109.

Reliability

Agreement between two raters completing the ONLS interview and the ODSS, and between four raters assessing the observed ONLS, was measured by counting the number of cases when raters disagreed.

An ICC between two raters' scores on the ONLS and ODSS were calculated using a one-way random effects model to allow direct comparison with previous reports of reliability of the ODSS questionnaire (Merkies et al. 2002a) and as values were identical to non-parametric weighted Kappa tests. Similarly, a two way random effects ICC was also calculated between the scores of four raters on the ONLS administered as an observed tool (Weir 2005).

Significance was set at $p < 0.05$ for all tests.

Responsiveness

Twenty four repeated measurements (n=19) on the ONLS and ODSS, and from 17 participants who were reassessed by one rater (the author) on the observed ONLS were tested using a two tailed Wilcoxon test to determine significant changes in scores.

As the data were assumed to be non-parametric, responsiveness was initially assessed using the median change in scores and the inter quartile range (Hamilton 1991). However, the median change on the ONLS, ODSS and the observed ONLS was zero, despite some

changes of 1 or 2 points. Therefore, responsiveness was estimated using the standardised response mean (SRM):

$$\text{SRM} = \frac{\text{Absolute mean change in score}}{\text{SD of mean change in score}}$$

A measure was considered to have good responsiveness if the SRM exceeded 0.8; moderate responsiveness was indicated by values from 0.5-0.8 (Cohen 1977).

The participant's perception of change in their abilities since their last measurement and any alteration in ODSS and ONLS scores was examined heuristically in 17 participants by counting the number of cases in which the direction of change in scores agreed with the individual's perception of change.

3.5. Results

3.5.1. Participants

One hundred participants, including four inpatients, were recruited. Their characteristics are shown in Table 3-1.

Table 3-1 Participant characteristics.

Participant characteristics n=100		
Gender (n)	Male	51
	Female	49
Mean Age, SD; range (years)	58	15.1; 19.7–83.1
Median ONLS scores, range	4	0-12
Median ONLS Obs, range (n=35)	4	0-11.5
Median ODSS scores, range	4	0-12
Diagnosis (n)	CIDP	41
	PDN	15
	GBS	12
	CIAP	12
	Other	20

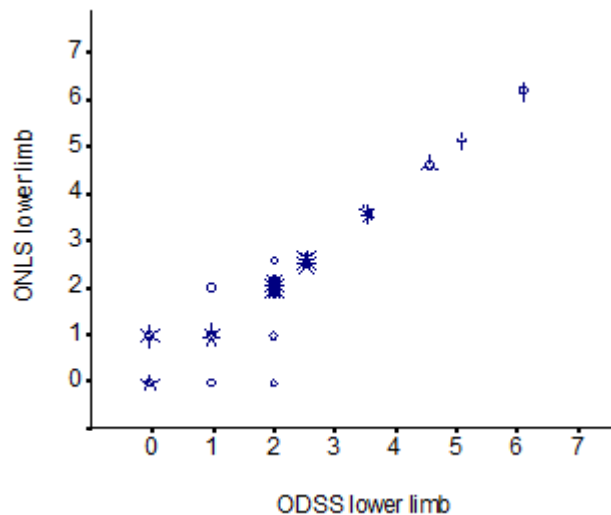
Observed ONLS scores (ONLS Obs) are median score and range for four raters. PDN - Paraproteinaemic demyelinating neuropathy; CIAP - Chronic Idiopathic Axonal Polyneuropathy. Other neuropathies included: Charcot-Marie-Tooth disease: 9, sensory multiple mononeuropathy: 5, mild generalised neuropathy: 3, vasculitic neuropathy: 2, idiopathic radiculomyelopathy: 1.

There were no significant associations between ONLS or ODSS scores and age or gender ($r < 0.3$). There were no significant differences between scores on the ONLS, observed ONLS and ODSS (Friedman test, $p = 0.12$).

3.5.2. Floor and ceiling effects

Two (2%) of the total scores (sum of lower and upper limb sections) on the ONLS and three (3%) on the ODSS were at the floor (highest available score, indicating maximal activity limitations) or ceiling (zero, indicating no activity limitations) of the scale. When lower limb section scores were examined, five participants scored zero (ceiling) on the lower limb section of the ODSS, indicating no activity limitations, but scored one, indicating some activity limitations, on the ONLS. This reflected the different lower limb scoring criteria and is shown in Figure 3-1.

Figure 3-1 Scatter plot to show relationship between ONLS and ODSS lower limb scores.



Lines at each point (sunflowers) represent multiple cases (n=100).

3.5.3. Validity

Face validity

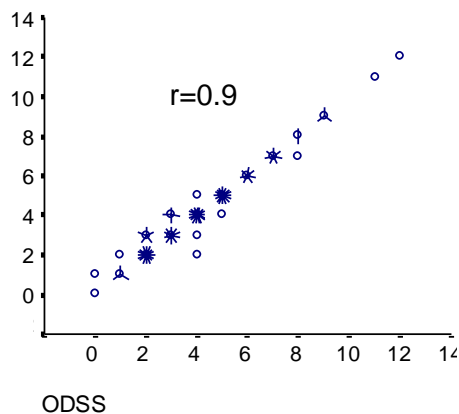
All consultant neurologists (n=16) independently preferred the ONLS to the ODSS and considered it appropriate for use in clinical practice. All considered the ONLS superior to the ODSS, 12 stated they would be interested in using the ONLS in their clinical practice and all reported that the ONLS reflected common activity limitations experienced by people with PN well (n=13) or very well (n=3).

Concurrent validity

There were no significant differences between the ONLS interview, observed ONLS and ODSS scores.

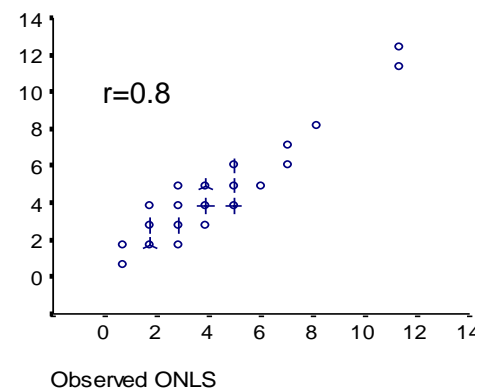
The ONLS questionnaire correlated closely with the ODSS ($r=0.97$, $p<0.001$) as hypothesised (H_1). The observed ONLS also correlated significantly with the standard ONLS ($r=0.86$, $p<0.001$) but was somewhat less strongly associated with the ODSS ($r=0.81$, $p<0.001$). Correlations between the ONLS and ODSS, and ONLS and ONLS observed are shown in Figure 3-2 and Figure 3-3.

Figure 3-2 Scatter plot to show correlation between the ONLS and ODSS



Lines at each point denote multiple cases (sunflowers), r = Spearman's rank correlation coefficient.

Figure 3-3 Scatter plot to show correlation between the observed and interview ONLS



$n=35$ for Observed and interview ONLS

The ONLS and ODSS had similar, moderate and significant correlations with the SF-36 physical function subscale ($r>0.6$) and strong associations with the RHS ($r>0.75$) shown in Table 3-2. As hypothesised (H_2), the ONLS (questionnaire and observed measure) did not correlate strongly with mental health or role limitation due to emotional problems subscale scores on the SF-36 ($r<0.4$). The associations between these measures and the ODSS were also weak ($r<0.4$).

The ONLS and ODSS demonstrated similar correlations with measures of strength and walking speed (MRC sum score, both ONLS and ODSS $r=0.6$, and ten metre walk times: ONLS $r=0.58$; ODSS $r=0.54$) whilst the ONLS had a somewhat stronger association with the Walk-12 questionnaire than the ODSS (ONLS: $r=0.65$, 95% CI: 0.48 to 0.77, ODSS: $r=0.43$, 95% CI: 0.21 to 0.61). Scores from the ONLS administered as an observed measure also demonstrated slightly weaker associations with the SF-36 physical function and Rotterdam handicap scales than the ONLS questionnaire, as predicted ($r=0.67$ and 0.63 respectively). These correlations are presented in Table 3-2.

Table 3-2 Scores and Spearman's rank correlations for the ONLS, observed ONLS and ODSS.

		Spearman's rank correlation coefficients (r)					
	Score	ONLS	p	ONLS Obs	p	ODSS	p
SF-36 : Physical Function	39 (0-80)	-0.65	<0.01	-0.63	<0.01	-0.66	<0.01
Mental health	72 (24-96)	-0.24	ns	-0.23	ns	-0.24	ns
Social function	60 (0-100)	-0.37	0.03	-0.37	0.03	-0.38	ns
Role limitation due to emotional problems	70 (0-100)	-0.013	ns	-0.09	ns	-0.004	ns
PCS	35.6 ±11	-0.55	<0.01	-0.54	<0.01	-0.56	<0.01
MCS	50 ±11	0.01	ns	0.01	ns	0.03	ns
10m walk time (n=70)	9.8 (14.5- 40)	0.58	<0.01	0.38	0.05	0.54	<0.01
MRC Score (n=97)	62 (16-70)	-0.62	<0.01	-0.72	<0.01	-0.6	<0.01
Walk-12 (n=65)	55 (20-100)	0.65	<0.01	-	-	0.43	0.03
Rotterdam Handicap Scale	30 (9-36)	-0.77	<0.01	-0.67	<0.01	-0.77	<0.01

n=35 unless otherwise stated, n=35 for all observed ONLS (ONLS Obs) correlations. Scores are median (range) except for physical and mental component summary scores (PCS and MCS) which are mean ±SD.

The ONLS and ODSS correlated strongly with each other in people with GBS and CIDP ($r=0.98$, $n=54$) and in those with other neuropathies ($r=0.96$, $n=46$). The scores on the ONLS from observation were similarly associated with other parameters and the ONLS questionnaire when examined in people with GBS or CIDP ($r=0.87$) and other PN ($r=0.84$).

The ONLS and ODSS also had similar associations with many of the other clinical measures in different forms of PN (Table 3-3). However, associations between the role limitation physical subscale of the SF-36 and the ONLS and ODSS were strong and statistically significant in people with GBS and CIDP ($r=0.65$, $p<0.01$), but weak and non significant in those with other PN (ONLS: $r=0.09$; ODSS $r=0.04$, both $p>0.05$). Strength measured using the MRC sum score also had weaker associations with ONLS and ODSS scores ($r=0.35$; $p<0.01$) in people with other neuropathies compared to people with GBS and CIDP ($r=0.85$; $p<0.01$). This is shown in Table 3-3.

Table 3-3 Association between ONLS and ODSS scores and measures of health status and participation for people with GBS or CIDP and other PN.

Spearman's rank correlations (r)					
		ONLS	p	ODSS	P
GBS and CIDP	SF-36 : Physical Function	-0.72	<0.01	-0.8	<0.01
	Mental health	-0.41	ns	-0.42	ns
	Role limitation due to emotional problems	-0.35	ns	-0.35	ns
	Role limitation due to physical problems	-0.65	<0.01	-0.65	<0.01
	MRC (n=50)	-0.87	<0.01	-0.87	<0.01
	10 m walk time (n=37)	0.54	<0.01	0.53	<0.01
	RHS	-0.82	<0.01	0.85	<0.01
Other PN	SF-36 : Physical Function	-0.65	<0.01	0.59	0.01
	Mental health	0.02	ns	0.17	ns
	Role limitation due to emotional problems	0.29	ns	0.34	ns
	Role limitation due to physical problems	-0.09	ns	-0.04	ns
	MRC (n=47)	-0.38	<0.01	-0.38	<0.01
	10 m walk time (n=33)	0.68	<0.01	0.63	<0.01
	RHS	-0.81	<0.01	-0.83	<0.01

n=17 for GBS and CIDP and n=18 for other PN unless otherwise stated. Ten metre walk times are measured in seconds. RHS- Rotterdam handicap scale.

3.5.4. Reliability

There was near perfect agreement between two independent raters who administered the ONLS and ODSS (ICC=0.97 for both). They agreed 19 times out of 20 on the interview ONLS and 18 times out of 20 on the ODSS.

On the observed ONLS, four different raters agreed in 18 cases from 35 (ICC=0.97). There were no significant differences between individual raters' scores. In the 17 cases where all raters did not agree, three raters agreed on nine cases and two raters agreed on the remaining eight cases.

Within professions, there were ten cases in which the scores between the consultant neurologists did not agree and eight cases where the scores between physiotherapists disagreed. Physiotherapists' and consultants' scores did not agree in eight cases.

There was perfect intra-rater agreement between the scores of one rater (the author) when film footage of ten participants performing the tasks outlined on the ONLS was rescored three months later.

When the median scores from four raters on the observed ONLS were compared with those from interview (n=35), 23 readings were within one point of each other. Nine individuals

reported greater activity limitations than were identified from observation of performance of the tasks on the ONLS, and three reported fewer activity limitations than were judged from observation.

3.5.5. Responsiveness

There were no significant differences between 24 repeated measurements on the ODSS and ONLS. Both tools measured similar changes after a mean of 31 weeks between measurements (range: three days to 52 weeks) as shown in Table 3-4.

The SRM of the ONLS questionnaire was 0.76 (95% confidence limits calculated using a 'bootstrap' technique² = 0.67 to 0.81) and the ODSS was 0.88 (0.8 to 0.95) (Efron 1979). The SRM for ONLS scores from observation was 0.83 (0.22 to 0.95).

When 17 participants were asked to identify any change in their abilities compared to previous measurements, seven patients felt they had deteriorated, five felt they had not changed since the previous measurement and five felt better. The ONLS scores detected these changes in only two cases and the ODSS in four cases. The median ONLS and ODSS scores on repeated measurements are shown in Table 3-4.

Table 3-4 Median scores for repeated measurements on the ODSS and ONLS.

	ONLS	ONLS Obs	ODSS
Measurement one	4 (1-7)	4 (1-6)	3.5 (1-7)
Measurement two	4 (1-6)	3.5 (1-5.5)	4 (1-6)

All values are median (range) for 24 repeated measurements on ONLS and ODSS and 17 measurements for the ONLS Obs. 17 from 24 participants were asked to rate the change in their health.

² Calculated by Dr A V Swan, statistician.

3.6. Discussion

The ONLS was derived from the ODSS to overcome a ceiling effect apparent on the lower limb scale in Chapter Two by including questions about running and climbing stairs. This study investigated the reliability, validity and responsiveness of the ONLS and the ODSS in people with PN.

The results demonstrated that the ONLS had similar reliability to the ODSS. However, the ONLS had better face validity and had a somewhat stronger association with mobility scores, measured by the Walk-12 questionnaire, than the ODSS suggesting improved sensitivity to mobility problems. The ONLS also had fewer scores at the ceiling (scoring zero) of the lower limb section ($n=8$, 8%) when compared to the ODSS ($n=13$, 13%) although both the ODSS and ONLS had scores within the recommended limits for floor and ceiling effects (McHorney 1998). The changes made to develop the ONLS also provided greater face validity; the ONLS has since been used as an outcome tool in a European randomised controlled trial of methotrexate in CIDP (RMC trial group 2009). However, the changes made to the ONLS appeared to somewhat reduce its responsiveness when compared to the ODSS (SRM: ONLS: 0.76; ODSS: 0.88), although the responsiveness of the ONLS was still considered moderate according to published criteria (Cohen, 1977).

Whilst the ODSS and ONLS could be considered to be representative indicators of ADL (Dittmar and Gresham 1997), a potential limitation of both scales is that they only comprise a restricted number of questions about common ADL which may not capture an individual's specific problems. There are several tools which specifically question mobility, including the Walk-12 investigated in Chapter Four. However, adapting the ODSS to include mobility items was considered preferable to using an additional tool to avoid increasing respondent burden, unless specific evaluation of mobility was required.

The suitability of the ONLS to measure activity limitations was supported by reports that climbing stairs is difficult for many people with PN, indicating it is an important activity to assess as it affects functioning both in the home and workplace (Erdmann et al. 2005). Similarly limitations in the ability to run are reported by over 24% (from 42) of people several years after GBS and could contribute to the reduction in leisure activities and sports reported after PN, indicating that assessing this ability is also important (Forsberg et al. 2004). The ability of the ONLS to measure these aspects of mobility was demonstrated in this study as ONLS scores were significantly and strongly associated with scores on the Walk-12 questionnaire ($r=0.65$) (Table 3-2).

This study utilised participants with a wider range of PN than those in the Merkies et al.'s (1999) original study of the ODSS. This aimed to increase the external validity of the findings and thus the clinical usefulness of both the ODSS and ONLS. The ONLS and ODSS demonstrated similar associations in people with GBS and CIDP and those with other PN on several clinical measures. However, the ONLS and ODSS did not correlate significantly with the SF-36 role limitation physical (RLP) subscale in neuropathies other than GBS and CIDP

(SF-36 RLP, $r < 0.1$). Both were also less strongly associated with strength (MRC sum score, $r < 0.4$; Table 3-3) in participants with other PN. Although these results should be viewed with caution because of the relatively small size of the subgroups, they suggest that people with GBS and CIDP are limited in a slightly different way to people with other PN. This finding also indicates that the tools used in inflammatory PN cannot always be assumed to be similarly valid in other PN. Consequently, the ONLS and ODSS should be used with appropriate caution in PNs other than GBS and CIDP until their properties have been investigated further.

The ONLS demonstrated slightly less responsiveness to change than the ODSS when evaluated from 24 repeated measurements of 19 individuals (SRM ONLS: 0.76; ODSS: 0.88). This finding is likely to be due to differences in scoring; a zero score on the ONLS lower limb scale requires no problems with running, walking or stair climbing whilst a zero score on the ODSS only requires no difficulty walking. This small difference makes it more difficult to improve from one to zero on the ONLS. Whilst the addition of these extra activities increased the validity of the ONLS, it appears to have reduced its responsiveness and so somewhat decreased its suitability to measure changes after treatment or interventions. This is a limitation which is common to many traditionally developed outcome tools, even when they are adapted, but may be remedied by newer, statistically orientated approaches to outcome tool development such as Rasch analysis (discussed on Page 123).

Interestingly, changes in the ODSS and ONLS scores did not concur with the participant's perception of change in their abilities (worse, same, better) in the majority of cases (ONLS: 2 from 17 cases; ODSS: 4 from 17 cases). This could be because the activities measured by the ONLS or ODSS did not examine areas that were important to participants. It is perhaps more likely that because responsiveness in this study was assessed in a small sample of outpatients who experienced relatively minor improvements and deteriorations in their clinical status, it was more difficult to detect an overall response. As participants were not undergoing large changes in their activities, they may have based their perception of change upon factors which are not measured on the ONLS or ODSS, including general and mental health. Others have reported greater agreement ($r = 0.67$) between ODSS scores and the participant's perception of change from 201 repeated measurements taken over one year in participants who were undergoing substantial changes in their functioning (Merkies and Schmitz 2006). Large responsiveness (SRM > 1) of the ODSS was also found (Merkies and Schmitz 2006). These participants were receiving treatment for CIDP or were recovering from GBS, and thus experienced larger improvements than participants in the current study, which is likely to influence the level of responsiveness.

Although the ONLS demonstrated moderate responsiveness, the somewhat stronger responsiveness seen on the ODSS deters from using the ONLS to measure change in future work (Cohen 1977). If the ONLS is to be used in future studies, its responsiveness would need to be re-examined in a larger group of people with PN who are experiencing changes in their activities to determine if it is able to measure change.

Observation of activities

The observed ONLS was designed to allow raters to observe participant activities, rather than ask people about how they would usually perform the tasks outlined by the questionnaire. An observed scale may be useful if an individual has difficulty communicating or there are other factors which may unduly influence the accuracy of their report. However, observation of performance may not be practical in a clinical environment and differences between the clinical and home setting may result in different levels of performance. This was shown by the less than perfect agreement between scores obtained by the questionnaire and observed ratings of people completing the tasks on the ONLS. This is consistent with report and performance of activities being influenced by factors in addition to physical capacity, including environmental and contextual aspects, motivation and personal variables (Schwartz and Spranger 1999; Wade 2001; World Health Organisation 2001). These results also indicate that the questionnaire and observed versions of the ONLS are not interchangeable.

The observed ONLS is complicated by the need for standardised equipment and by reduced inter-rater reliability. The reduced reliability seen in this study (17 from 35 cases were not agreed by all four raters) is likely to be because the observed score is dependent upon the rater's subjective opinion of the quality of the performance of the tasks and raters were not provided with formal training regarding the scoring of the observed ONLS. Whilst training is recommended to optimise the reliability of outcome measurement, it significantly increases administrator burden (Ottenbacher et al. 1996). Inter-rater reliability may have also been reduced in this study as participants were filmed and so raters could not adjust their position to obtain a clearer view of the tasks being performed.

In light of these limitations, the questionnaire version of the ONLS should be used in preference to the observed ONLS. As relatively few people with PN had difficulty completing the questionnaire ONLS in this study, the value of further work to refine the observed version of the ONLS is unclear. If an observed outcome tool was required, further work including formal assessor training and re-investigation of the reliability of the observed ONLS in a range of patients with PN would be needed. Alternatively, future work could seek to investigate the suitability of other tools based on observation or proxy report, such as the Frenchay Activities Index, for people with PN (Tooth et al. 2003).

3.6.1. Limitations

The conclusions from this study are limited by a number of factors. Both the ONLS and ODSS questionnaires are based upon respondent's report, and so may be affected by a range of personal, social and environmental factors, a desire to please the rater and by phenomena including response shift. Response shift (also discussed in Chapter One, Page 44) occurs when an individual recalibrates their perceptions and standards to accommodate to changes in their health and affects the accuracy of report (Spranger and Schwartz, 1999). These factors are inherent to all tools which rely upon participant report but should be considered when viewing the data they yield.

The ONLS and ODSS were developed without direct involvement of PN patients. This means that the items, whilst generic, may not be the most appropriate or relevant to this patient group. Whilst this is a limitation common to many tools, patient and public involvement (PPI) would allow new tools to be developed that reflect the key issues faced by people with PN and increase their suitability for research and clinical use (INVOLVE 2012).

The small sample utilised in some sub group analyses, such as the estimation of responsiveness and measurement of validity in different diagnostic groups, reduced the external validity of the findings. As the raters were the authors of the ONLS, their expectations are likely to have introduced bias in the collection and interpretation of data. The assessment of face validity is also likely to be biased as it was based upon the answers of neurologists whose opinions may be influenced by a desire to please the authors of the ONLS. Although this is a limitation of the evaluation of many published outcome tools, it suggests that independent investigation of the ONLS is warranted if it is to be used more widely.

3.7. Conclusion

This study modified the ODSS to produce the ONLS outcome tool to measure common activity limitations experienced by people with PN. Both were evaluated in a wide range of PN. The ONLS correlated well with the ODSS, retaining the simplicity of this tool whilst improving its ability to measure minor lower limb limitations. This also reduced the number of scores at the ceiling of the scale. This provided the ONLS with better face validity, supporting its use over the ODSS. The ONLS also demonstrated a strong association with the Walk-12, indicating it was able to better reflect aspects of mobility than the ODSS. However, the ODSS demonstrated a slightly higher level of responsiveness than the ONLS which deters from using the ONLS to measure change. Further work is necessary to re-examine the responsiveness of the ONLS in a larger sample undergoing greater changes in their functioning before it can be used in clinical settings, as it appears that the improved ability to measure mobility problems gained by refining the lower limb criteria has inadvertently reduced its ability to reflect change.

Despite several similar strength correlations with the SF-36 and its subscales and other tools in all participants, the ONLS and ODSS were only significantly associated with the role limitation physical subscale of the SF-36 in GBS and CIDP and not in other PN. Although this may be an artefact of the sample size, this indicates that people with different PN may be affected somewhat differently and that similar validity of the ODSS and ONLS cannot be assumed in all types of PN.

The ONLS observed scale developed here could be used as an alternate measure of activity limitations in people with PN, but is only recommended if the ONLS questionnaire cannot be used. Scores between observed and questionnaire versions are not interchangeable, which confirms that self report is influenced by a range of factors not captured by observation.

The ONLS now requires independent evaluation in other patient settings in comparison to other validated ADL tools and in different groups of PN. Future work should also seek to develop new measures of activity limitations and/or evaluate other activity limitation tools to overcome the shortcomings of the ODSS and ONLS.

3.8. Postscript: developments since 2009

In 2011, Van Nes et al. published a patient based linear scale of activity limitations for people with PN, developed using Rasch analysis (Bond and Fox 2007; van Nes et al. 2011). This was developed to overcome limitations in the existing tools measuring activity limitations in people with PN which are based upon expert consensus (van Nes et al. 2011). Traditional outcome tools require respondents to complete all items, even if some are irrelevant and assume that all items are equally weighted. Rasch developed tools use the probability of a specified response to eliminate redundant items and provide a true unidimensional, linear scale. Items on the new tool for people with PN, called the Rasch built Overall Disability Scale (R-ODS) were derived from the International Classification of Functioning, literature search and patient interviews. Respondents indicated if they had no difficulty (2), some difficulty (1) or were unable to do (0) a range of activities including eating, brushing their teeth and turning a key in a lock. These initial questionnaires were sent to people with a clinically stable immune mediated polyneuropathy who also completed the ODSS. Two hundred and ninety four people returned the questionnaires (GBS:174, CIDP:80, Monoclonal gammonopathy: 40). Rasch analysis of their responses refined the original 146 items to 24 which formed the R-ODS. Scores from the R-ODS had acceptable ceiling effects (5.8%), correlated strongly with the ODSS ($r=0.85$) and appeared reliable (ICC >0.9). Items derived from Rasch analysis which appear on the R-ODS, but are not measured on the ODSS, include the ability to run and climb stairs which further supports their inclusion in the ONLS. Whilst the R-ODS has more items than both the ODSS and ONLS it is still likely to have an acceptable burden. The R-ODS has advantages over the ONLS and ODSS as it is able to measure a wider range of activities, has fewer redundant items and demonstrates similar validity and reliability. The performance of the R-ODS now requires independent evaluation in patient groups outside the Netherlands and its responsiveness must be established if it is to be used to indicate change.

Chapter 4. Measurement of mobility in people with peripheral neuropathy

4.1. Summary

Many people with inflammatory peripheral neuropathies (PN) experience difficulty with mobilising. In this Chapter, the properties of three different outcome tools were investigated to determine if they were suitable to reflect aspects of ambulant mobility in people with PN.

Study One: The Walk-12 measures an individual's perception of their mobility and was investigated in a prospective study of 65 patients with PN. The Walk-12 was valid as it demonstrated several strong correlations with other tools ($r = 0.72$ with SF-36 Physical component summary score and $r = 0.86$ with SF-36 Social Function score, all $n = 15$; $r = 0.77$ with ONLS lower limb subscale, $n = 50$) and was internally consistent (Cronbach's alpha $\alpha = 0.96$, $n = 61$) and reliable (test re-test reliability ICC = 0.96, $n = 12$). Although originally designed for people with multiple sclerosis (MS), this study indicated that the Walk-12 could be used to measure self-reported wider mobility in ambulant people with PN if its responsiveness can be established.

Studies Two and Three: The physiological cost index (PCI), was originally designed as a quick and low technology measure of the energy used whilst walking. However, the optimal dimensions of the track used to measure the PCI and the properties of the PCI in PN have not been determined. In Study Two, PCI values in 40 healthy participants measured on two differently shaped tracks were compared. The results showed that a 20 metre figure of 8 track facilitated a faster self-selected walking speed than a 12 metre figure of 8 track (mean \pm SD self-selected walking speed on 20 m track = 70.7 ± 13 metres min^{-1} ; 12 m track = 63.2 ± 12 metres min^{-1}). Studies Two and Three also examined the validity of the PCI and compared results to a new adaptation of the PCI, the mPCI using energy cost (EO_2) as a criterion measure of the energy used whilst walking. Responsiveness of the mPCI and PCI was assessed using changes in 14 PN participants from the exercise intervention in Chapter Two. The results showed that the PCI had limited validity (correlations with EO_2 were $r = 0.03$ and $r = 0.21$ in healthy and PN participants respectively) and demonstrated large variability on repeated measurements. The mPCI showed greater validity than the PCI in both healthy and PN participants as correlations with EO_2 were somewhat stronger ($r = 0.34$ and $r = 0.87$ in healthy and PN participants respectively) and discriminated between participants who walked independently and those who used walking aids. It also had better responsiveness than the PCI (mPCI: SRM: 0.62, PCI: 0.27).

Further work is necessary to confirm the properties of the Walk-12 in inpatients with PN, assess its responsiveness and determine the test re-test reliability and responsiveness of the

mPCI in a larger sample of people with PN. However, both are promising tools to measure meaningful aspects of mobility in people with inflammatory PN.

The studies in this chapter have been published and full papers are appended to this thesis:

Graham, R.C., Smith, N.S., White, C.M. The reliability and validity of the physiological cost index of walking in health participants when walking on two tracks. *Arch Phys Med Rehab* 2005 Vol. 86, p. 2041-2046

Graham, R.C., Smith, N.S. White, C.M. An investigation of the physiological cost index of walking. *Abstract*, International Society for Posture and Gait Research proceedings. Gait and Posture. 2005 Vol. 21, S1; S147

Graham, R.C., Smith, N.S. White, C.M. The reliability and validity of the physiological cost index on two different tracks. *Abstract Clin Rehabil* 2005 Vol. 19, p 576 -577

Graham, R.C., Hughes, R.A.C. Clinimetric properties of a walking scale in peripheral neuropathy. *Journal of Neurol Neurosurg Psychiatry* 2006 Vol. 77, p 977-979

4.2. Background

Mobility describes a number of ways of moving including walking, changing positions and moving effectively in normal surroundings (World Health Organisation 2001). Normal mobility is a complex activity. It depends upon an integrated nervous system to provide sufficient motor drive and sensory feedback to allow smooth progress of the body through space, using the smallest amount of energy possible (Prince et al. 1997; Waters and Mulroy 1999). Difficulty mobilising is a significant feature of many neurological conditions, including PN, and so is a frequent focus of rehabilitation (Lord et al. 1992; Pearson et al. 2004).

As discussed in Chapter One, the majority of people with inflammatory PN will maintain or regain the ability to walk but will have some residual difficulties. Common persistent mobility problems in PN include reduced walking speed, difficulty running, and difficulty walking long distances and outside (Busse et al. 2006; Erdmann et al. 2005; Forsberg et al. 2004; Forsberg et al. 2005; Lennon et al. 1993). In one small survey, 80% (of 12 people) with CIDP reported difficulty climbing stairs and running whilst almost a quarter (24% of 42) of people after GBS remained unable to run several years after nadir (Erdmann et al. 2005; Forsberg et al. 2004).

4.2.1. Measuring mobility

A person's ability to ambulate influences their capacity to perform simple activities of daily living and to interact within the wider community (Chiou and Burnett 1985; Lord et al. 2004). Changes in mobility often indicate disease progression or improvement in response to a range of treatments, including rehabilitation, yet there is no standard way of measuring an individual's usual ambulation (Pearson et al. 2004).

The time taken to walk a specified distance (often ten metres) is a commonly used indicator of mobility. As reported in Chapter One, ten metre walk times are considered reliable and responsive in people with a range of neurological conditions, including PN (Merkies et al. 2003a; Rossier and Wade 2001; Salbach et al. 2001; van Loo et al. 2003). However, the ten metre walk times of PN participants were not significantly different from baseline after the exercise intervention (Chapter Two) despite significant improvement in reported physical functioning. Whilst this may indicate that mobility was not affected by the intervention, it could also be because an assessment of walking speed over a short distance in a safe, well lit, standard environment does not reflect usual walking performance (Thies et al. 2005). This indicates that other tools that directly measure aspects of a participant's usual mobility should be considered for people with PN.

Measurement of self-reported mobility

In contrast to objective measurement of walking, self-reported mobility indicates perceived functioning in a respondent's usual environment. It is already measured by some activity and participation tools in PN (e.g. the Overall Disability Sum Score, ODSS, and Rotterdam Handicap Scale, RHS) (Merkies et al. 2002a; Merkies et al. 2002b) but items typically focus upon the assistance or aids required to walk and do not question other aspects of mobility

such as effort and quality of walking. Whilst these features are beyond the scope of a global activities of daily living scale (ADL) they may influence mobility in the community and independence and so warrant measurement (Lord et al. 2004; Rossier and Wade 2001; Shumway-Cook et al. 2002).

One tool that reflects wider aspects of mobility is the multiple sclerosis walking scale (MSWS-12 or Walk-12). This self completed questionnaire was designed to capture aspects of mobility reported by people with MS (Hobart et al. 2003). The Walk-12 contains items about stairs, indoor and outdoor mobility and it also questions distance and the effort of walking. It does not measure non-ambulant mobility (such as turning in bed) which are unaffected in the majority of people beyond the acute illness or with a chronic PN (Forsberg et al. 2004). The Walk-12 has 12 items scored on a five point Likert scale and is reported to be quick and easy to complete (Hobart et al. 2003). Since the development of the Walk-12, its properties have been evaluated in 120 people with a range of neurological conditions and shown to be acceptable, valid and reliable (Holland et al. 2006). This supports its use in PN, although it was not responsive to changes after rehabilitation in people with spinal cord injury (Holland et al. 2006). Despite being developed for people with MS, all items also appear suitable to capture common mobility limitations in PN including stair climbing, walking on uneven surfaces and running. Therefore, the validity, reliability and responsiveness of the Walk-12 in people with PN were investigated in Study One in this Chapter.

Measurement of the energy used when walking

People with PN often have decreased muscle strength, poor balance, reduced sensation and/or reduced aerobic fitness which increases the energy used when mobilising (Mueller et al. 1994; Pearson et al. 2004; Thoumie and Mevellec 2002). These increased energy demands can reduce walking distance or prevent walking in some environments, which indicates that measurement of energy use is warranted in this patient group (Boyd et al. 1999; Brehm et al. 2006; Waters and Mulroy 1999). Energy usage can be measured most accurately by direct or indirect calorimetry. However, both systems are expensive, cumbersome and are not available in the majority of clinical settings. The Physiological Cost Index (PCI) and modified PCI (mPCI) are low technology, low cost alternatives which could be used to measure the energy used whilst walking in people with PN if their validity, reliability and responsiveness can be established (MacGregor 1979). Therefore, Studies Two and Three in this chapter investigated the properties of the PCI and mPCI as potentially cheap and simple alternative measurements of energy use when walking in healthy and PN participants.

4.3. Objective

The overall objective of the studies in this Chapter was to examine the validity, reliability and responsiveness of the Walk-12, PCI and mPCI outcome tools as measures of mobility in people with PN.

4.4. Study One - The validity and reliability of the Walk-12 questionnaire for people with peripheral neuropathy

4.4.1. Aim

The aim of this study was to investigate the validity and reliability of the Walk-12 to measure self reported mobility in people with PN.

4.4.2. Background

The MS walking scale, renamed the Walk-12, questions self-perceived mobility (Hobart et al. 2003). The Walk-12 is completed by the respondent. It has 12 items which are answered using a Likert scale (1-5, shown overleaf). It contains items which question mobility activities including walking, running and stair climbing. Overall scores are calculated using the equation:

$$\text{Walk - 12 score} = \left[\frac{\text{Total score} - \text{minimum score (12)}}{\text{Maximum score possible} - 12} \right] \times 100$$

A higher score indicates greater limitation in mobility and walking ability (Hobart et al. 2003; Holland et al. 2006).

The Walk-12 measures the respondent's perceived limitations of their mobility due to their condition and was generated for people with MS from patient interview, literature review and expert opinion (Hobart et al. 2003). It has demonstrated excellent internal consistency (Cronbach's $\alpha = 0.97$) and test re-test reliability (ICC=0.94) in over 400 people with MS (Hobart et al. 2003). It was also valid and internally consistent in two hospital based samples (n=132) and responsive to change after treatment (effect size=0.93) (Hobart et al. 2003). The internal consistency, validity and responsiveness of the Walk-12 were independently confirmed in community based participants and outpatients with MS (McGuigan and Hutchinson 2004) and have been investigated in 120 inpatients after spinal cord injury (SCI) and stroke (Holland et al. 2006). In these groups, the Walk-12 was broadly appropriate, internally consistent and responsive although responsiveness was less in spinal cord injured participants and test re-test reliability was not assessed (Holland et al. 2006).

There are no validated measures of self-reported mobility used in PN currently despite these data being useful in increasing understanding of functioning. Although PN and MS are very different, the similarities of activity limitation and favourable properties of the Walk-12 in other neurological groups indicate that it deserves consideration in PN. The items on the Walk-12 are generic functions, irrespective of neurological diagnosis, further supporting its evaluation in PN. It also has good face validity, as it examines limitations in mobility which many people with PN clinically report as troublesome. It also provides indications of usual functioning in the community, which are not captured by objective, clinically based measurements.

Outline of the Walk-12 questionnaire

The Walk-12 questionnaire, given to participants, is shown overleaf.

Walking Scale Questionnaire (Walk-12)

These questions ask about limitations to your walking due to peripheral neuropathy *during the past 2 weeks*

For each statement please circle the **one** number that best describes your degree of limitation. Please answer **all** questions even if some seem rather similar to others, or seem irrelevant to you. If you cannot walk at all please tick this box ☐

In the past 2 weeks how much has your peripheral neuropathy...	Not at all	A little	Moderately	Quite a bit	Extremely
Limited your ability to walk?	1	2	3	4	5
Limited your ability to run?	1	2	3	4	5
Limited your ability to climb up or down stairs?	1	2	3	4	5
Made standing when doing things more difficult?	1	2	3	4	5
Limited your balance when standing or walking?	1	2	3	4	5
Limited how far you are able to walk?	1	2	3	4	5
Increased the effort needed for you to walk?	1	2	3	4	5
Made it necessary for you to use support when walking indoors e.g. holding on to furniture, using a stick etc.?	1	2	3	4	5
Made it necessary for you to use support when walking outdoors e.g. using a stick or frame etc.?	1	2	3	4	5
Slowed down your walking?	1	2	3	4	5
Affected how smoothly you walk?	1	2	3	4	5
Made you concentrate on your walking?	1	2	3	4	5

Please check you have circled **one** number for each question.

Please hand this to the doctor at the start of your consultation.

Thank you for completing this questionnaire.

© adapted from 2000 Neurological Outcomes Measurement Unit

4.4.3. Method

A cross-sectional design was used to investigate the concurrent validity, internal consistency and test re-test reliability of the Walk-12 in people with PN (Sim and Wright 2000).

Fifteen volunteers with inflammatory PN were initially recruited from the Peripheral Nerve clinic at Guy's Hospital, London, and from a volunteer database of participants from previous research at King's College London (Group One). Local ethical approval was granted by Guy's and St Thomas's Hospital research ethics committee and participants gave informed consent. All attended King's College London for testing on one occasion. A subgroup of 12 participants returned for re-measurement one week later.

After initial investigation in this group (Group one), the Walk-12 was incorporated into routine clinical assessment of outpatients attending the Peripheral Nerve clinic at Guy's Hospital. With local audit committee approval, the properties of the Walk-12 were examined in 50 patients attending the clinic (Group two). All participants had a secured diagnosis of PN and were ambulant for at least some part of the day.

Measurement

Group One

All participants (n=15) completed the Walk-12, SF-36, ODSS and RHS questionnaires in a quiet room (Merkies et al. 2002a; Merkies et al. 2002b; Merkies et al. 2002c). The times taken to walk ten metres at both preferred and fast pace were recorded (Merkies et al. 2003a; van Loo et al. 2003). The MRC sum score was used to grade muscle strength (Kleyweg et al. 1991). All data were collected by a chartered physiotherapist (the author) who was experienced in grading muscle strength and data collection in this patient group.

Group Two

All participants (n=50) completed the Walk-12, ODSS and ONLS questionnaires. Muscle strength was measured using an adapted form of the MRC sum score, expanded to include the first dorsal interosseous muscles and scored from a maximum of 70 by an expert neurologist (Professor R.A.C. Hughes). Participants were timed as they walked ten metres, as fast as they safely could (van Loo et al. 2003). The ODSS, ONLS, MRC sum score and timed ten metre walk were recorded during routine clinical examination by a consultant neurologist whilst the Walk-12 was completed by the patient in the waiting area prior to consultation.

4.4.4. Analysis

Any uncompleted items on the Walk-12 were replaced by the mean of that individual's completed items (Hobart et al. 2003). If less than 50% of items (six items) were completed, the individual's data were excluded (Hobart et al. 2003). The Walk-12 was transformed to a 0-100 scale as shown on Page 128.

The ceiling (zero, indicating no limitations) and floor effects (100, indicating maximal limitations) for total Walk-12 scores were examined and the mean score on each item was calculated.

Raw questionnaire data were assumed to be non-parametric due to the ordinal nature of the scales. Transformed questionnaire and all other data were investigated for normality using Kolomogorov Smirnov tests and by examining frequency histograms. Parametric or non-parametric statistics were then used as appropriate.

Validity

The concurrent validity of the Walk-12 was investigated by measuring associations with other outcome tools.

In Group one (n=15), Pearson's or Spearman's rank correlation coefficients between the Walk-12 and values from the SF-36, ODSS and ten metre walk times were calculated. It was hypothesised that:

H₁: *Convergent validity*: Walk-12 scores would be strongly and significantly associated with the SF-36 physical function (PF) subscale and the physical component summary score (PCS).

H₂: *Discriminant validity*: associations between Walk-12 scores, mental health (MH) subscale and mental component summary scores (MCS) of the SF-36 would be weak and considerably lower than the associations between the Walk-12 and PF and PCS.

In group 2 (n=50), Spearman's rank correlation coefficients were calculated between the Walk-12, the upper, lower limb section and total scores on the ONLS and ODSS, the expanded MRC sum score and ten metre walk times. It was hypothesised that:

H₃: *Convergent validity*: ONLS lower limb scores and the Walk-12 would be strongly and significantly associated.

H₄: *Discriminant validity*: associations between the Walk-12 and the upper limb scores on the ONLS and ODSS would be weak and considerably smaller than the associations between the lower limb scores and Walk-12.

The null hypothesis for both groups was:

H₀: There would be no significant associations between Walk-12 scores and scores on the SF-36 nor between the Walk-12 and ONLS upper limb scores.

Correlation coefficients were compared to test these hypotheses and were judged to be low/weak ($r=0.1-0.3$), moderate ($r=0.3-0.6$) or large/strong ($r>0.6$) according to published criteria (Cohen 1977).

Divergent validity was assessed by examining the ability of scores on the Walk-12 to discriminate between participants who used walking aids and those who did not using an independent t test (two tailed, assuming unequal variance) for the entire cohort (n=65).

Reliability

The internal consistency of the scale was assessed using Cronbach's α (alpha) reliability coefficient (Huck 2004b). A high value of α (usually greater than 0.7) indicated that the scale had good internal consistency and that all items assessed the same construct (Huck 2004b).

The test re-test reliability of the Walk-12 was assessed by comparing two repeated measurements in 12 participants in group one, recorded one week apart. Agreement between repeated measurements was examined using a two way fixed intra class correlation coefficient (Weir 2005) and by calculating the standard error of the measurement (SE_m) from:

$$SE_m = \sqrt{MS_w}$$

where MS_w – mean squares of within subject variability (Weir 2005).

The SE_m provides an index of reliability, but is independent of between subject variability (Weir 2005).

Two tailed significance was set at $p < 0.05$ for all tests.

4.4.5. Results

Participant characteristics and mean Walk-12 scores are shown in Table 4-1. Sixty one from 65 participants fully completed the Walk-12. Missing data were able to be substituted by the average score reported by remaining participants in all cases as respondents only omitted one item.

Table 4-1 Participant characteristics for groups 1 and 2

Participant characteristics	Group 1 (n=15)	Group 2 (n=50)
Mean age, years	50.7 ±11 (25-70)	57.7 ±15.5 (20-84)
Gender	11 male, 4 female	27 males, 23 females
Diagnosis	GBS:7, CIDP:6, MMN:1, PDN:1	GBS:11, CIDP:20, CIAP:4, PDN:6, Other:9
Walk-12 scores	37.5 ±22.6 (0-69)	48.3 ±33 (0-100)

Age and Walk-12 scores displayed as mean ±SD (range). Other neuropathies in group two included: vasculitic neuropathy: 3, CMT: 3, sensory multiple mononeuropathy: 2, idiopathic radiculomyelopathy: 1. A higher Walk 12 score indicated greater limitations.

Description of mobility reported by people with PN

The mean score on each question on the Walk-12 for all participants (n=65) is shown in Figure 4-1. Participants with PN reported limitations on all items on the Walk-12. As can be seen in Figure 4-1, they reported most difficulty with running, walking longer distances, smooth walking and walking quickly and required increased concentration and effort while walking.

The Walk-12 questionnaire had excellent internal consistency (Cronbach's $\alpha=0.96$, n=61). There were no significant associations between age and Walk-12 scores in the entire cohort ($r=0.03$, n=65).

Group One

Participants in Group one completed all items on the Walk-12 (Table 4-1). Whilst two (13.3%) participants scored zero (indicating no limitations), no one scored at the floor of the scale (100, indicating maximum limitations).

Validity

Correlations between the Walk-12 and other questionnaire scores are shown in Table 4-2.

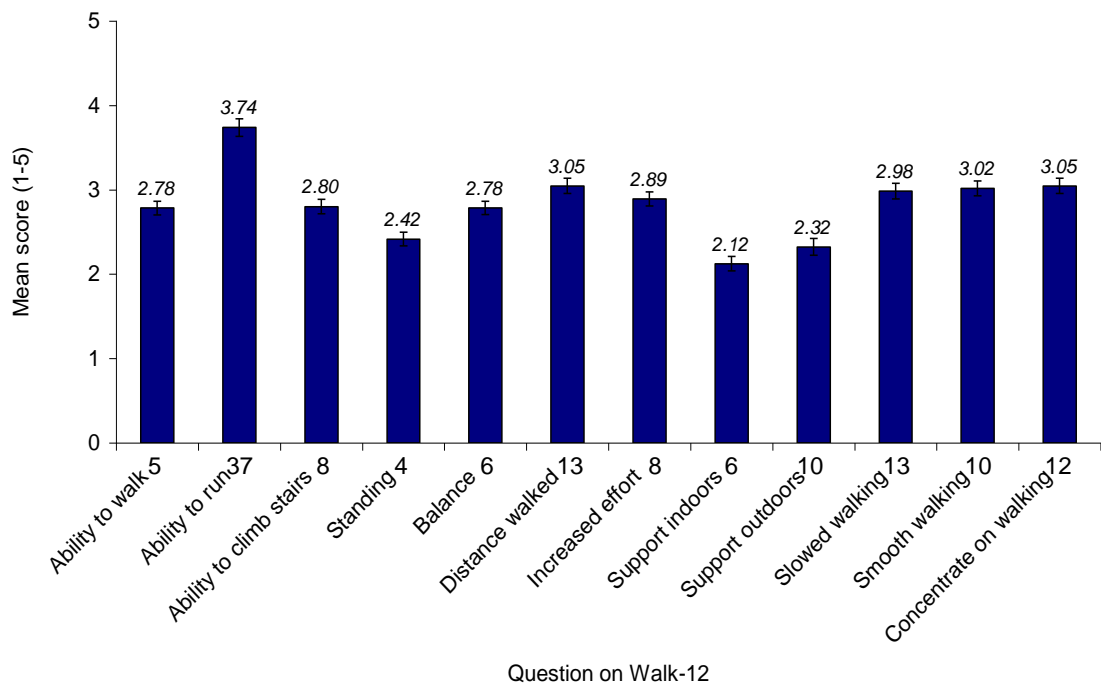
As predicted in H₁, the Walk-12 demonstrated convergent validity as scores were strongly and significantly associated with physical function and performance measured on the SF-36 PF and PCS. Furthermore, correlations with the SF-36 MH and MCS scores, also shown in Table 5-2, were weak and not statistically significant, showing discriminant validity.

Reliability

Test re-test reliability was assessed on a sub group of 12 participants (10 males) who completed the Walk-12 on two occasions, one week apart. Mean (SD) Walk-12 scores were

similar between session one (31.2 ± 26.3) and session two (29.5 ± 24) and the test re-test reliability was high ($ICC=0.96$, $SE_m=5$).

Figure 4-1 Chart to show mean scores on each question of the Walk-12.



Error bars show the standard error of the mean for each item. Mean scores for each item are shown in italics. Numbers under x axis denote the number of participants who reported maximal limitations (5) on each item.

Group Two

Forty-six from 50 patients completed all Walk-12 items appropriately. Four patients missed out one item. Eight patients (16%) scored zero on the Walk-12 and two (4%) scored 100. Mean Walk-12 scores, MRC sum score, ten metre walk times and scores on the ODSS and ONLS are displayed in Table 4-2.

Validity

As predicted by H_3 , the Walk-12 correlated significantly and most strongly with the ONLS lower limb scores (Table 4-2), demonstrating convergent validity. Walk-12 scores also demonstrated moderate significant associations with ten metre walk times and the total ONLS. Only a weak correlation was seen between the ODSS lower limb score and the Walk-12.

Divergent validity was demonstrated as correlations with the upper limb scores on the ONLS and ODSS were weak (accepting H_4) and an independent t test revealed that scores on the

Walk-12 could discriminate between patients who used walking aids (mean \pm SD: 63.3 \pm 14.4, n=21) and those who did not (27.2 \pm 22.7; n=44 p<0.001).

Table 4-2 Walk-12 scores, and correlations with the ODSS, Rotterdam handicap scale and SF-36 questionnaire subscales.

Group 1 n=15	Score	Correlation coefficient (r)	p
Walk-12	37.5 \pm 22.6 (0-68.7)	-	-
SF-36: PCS	45.1 \pm 10.3 (28.5-58)	-0.72*	0.003
MCS	57.4 \pm 4.9 (48.2-63.2)	-0.4	ns
PF	75 (30-100)	-0.82*	0.001
RLP	100 (0-100)	-0.42	ns
RLM	100 (100-100)	-	-
Social function	55.6 (0-100)	-0.86*	<0.001
MH	88 (64-100)	-0.45	ns
Energy and vitality	60 (20-95)	-0.64*	0.01
Pain	77.8 (33.3-100)	-0.71*	0.003
Health perception	72 (25-92)	-0.65*	0.009
Health transition	50 (0-100)	-0.5	0.06
ODSS	2 (0-5)	0.81*	0.001
Rotterdam handicap scale	35 (22-36)	0.6*	0.03
Group 2 n=50			
Walk-12	48.3 \pm 33 (0-100)	-	-
ONLS upper limb	2 (0-4)	0.30*	0.05
ONLS lower limb	2 (0-5)	0.77*	<0.001
ONLS total	4 (0-9)	0.67*	<0.001
ODSS upper limb	2 (0-4)	0.31*	0.02
ODSS lower limb	2 (0-5)	0.36*	0.01
ODSS total	4 (0-9)	0.36*	0.01
MRC sum score n=49	64 \pm 7.9 (32-70)	-0.28*	0.05
Ten metre walk time (seconds) n=42	9.8 \pm 6.7 (4.6-40)	0.63*	0.001

All values are medians (range) except for the Walk-12, MRC sum score, PCS, MCS and 10 metre walk time which are mean \pm SD (range). All correlations were calculated using Spearman's rank except for correlations between the MRC, PCS, MCS, 10 metre walk test and Walk-12 scores which are Pearson's correlations. A higher score indicates greater restriction in activities on all scales. * denotes a significant correlation with the Walk-12 at p<0.05.

PCS- Physical component summary score, MCS- Mental component summary score, PF- physical function, RLP – role limitation physical, RLM – Role limitation due to emotional problems, MH – mental health SF-36 subscales.

4.4.6. Discussion

The aim of this study was to investigate the suitability, internal consistency, test re-test reliability and validity of the Walk-12 questionnaire in people with PN (Hobart et al. 2003). The results show that people with PN reported most difficulty running and moderate difficulty walking smoothly, walking over longer distances, walking at a faster speed. Participants also reported that they required greater concentration when walking.

The Walk-12 was quick and straightforward to complete. Only four participants omitted one item from the Walk-12, and total scores for all participants were able to be calculated by adjusting for missing items. Ten participants (from 65) had scores at the ceiling of the range, indicating no reported limitations in mobility. Two participants scored at the floor of the scale (indicating maximum limitations in mobility). These levels indicate that Walk-12 was largely well targeted to the level of self-reported mobility for the majority of people with PN in this sample. Cronbach's alpha was high (0.96) indicating that the Walk-12 measured a single consistent construct in people with PN, and that it was reasonable to score the Walk-12 by summing all items (Huck 2004b).

Validity

The magnitude and pattern of correlation with other data collection tools provide support for the validity of the Walk-12 in the study sample. As predicted, the Walk-12 correlated strongly with indicators of reported physical function and lower limb functional ability, but weakly with reported mental health and upper limb function (shown in Table 4-2). Similar findings have been reported in people with MS (Hobart et al. 2003). Participants who used walking aids had significantly higher scores on the Walk-12 than those who did not, indicating that the scale could discriminate between these two states.

The Walk-12 correlated strongly and significantly with lower limb scores on the ONLS scale ($r=0.77$) but had only a weak, albeit significant association with lower limb scores on the ODSS ($r=0.36$). This was anticipated as, although the ODSS and ONLS differ on only one item in the lower limb category, the ONLS was specifically designed to be more sensitive to the presence of minor lower limb restrictions (as described in Chapter Three) and included some similar activities to the Walk-12.

Of all the outcome tools that correlated with the Walk-12, the social function subscale scores of the SF-36 demonstrated the strongest association, accounting for 74% of its variance ($r=0.86$). As items on the Walk-12 do not directly question social functioning, this strong association indicates that the Walk-12 reflected the influence of mobility upon social participation. This enhances its clinical usefulness.

From data routinely collected in the host outpatient clinic (MRC sum score, ten metre walk time, ODSS and ONLS) the strongest association with scores on the Walk-12 was with the lower limb section of the ONLS. However, this only explained 59% ($r=0.77$) of the variance of the Walk-12, indicating that the Walk-12 could add valuable information to assessment for people with PN in clinical and research settings.

The composition of the sample did not allow comparison of the validity of the Walk-12 between GBS and CIDP and other PN as the majority of participants had either a diagnosis of GBS or CIDP (77%; n=50). All participants in this study were also outpatients. Consequently, the properties of the Walk-12 require further evaluation if it is to be used in inpatients or in other PN. Others have noted that there is considerable floor effect (scores indicating maximal limitations) on the Walk-12 in inpatients after stroke, spinal cord injury or with MS, although this was not evident at discharge (Holland et al. 2006). This implies that the Walk-12 might not be suitable for people with PN who experience severe mobility limitations, those during the acute phase of GBS or an exacerbation of CIDP when inpatient rehabilitation is required. In these situations, other tools which measure more severe limitations including reduced bed mobility and transfers would be more appropriate.

Reliability

Test re-test reliability of the Walk-12 was high (ICC= 0.96), but this should be viewed with some caution as the sample in which it was measured was small (n=12), comprising only those participants able to return for reassessment, which reduced its external validity.

4.4.7. Limitations of the study

The findings of this investigation are limited by a number of factors. As the study was not blind, the expectations of the investigator could influence results although this was minimised by participants completing questionnaires independently. The nature of the study sample restricts the external validity of the findings as the majority of people had GBS or CIDP, were outpatients and had to be ambulant for at least some part of the day. This means that the results cannot be automatically applied to other forms of PN and the Walk-12 cannot be assumed to be suitable for people with PN who experience severe mobility limitations or those during the acute phase of GBS or an exacerbation of CIDP when inpatient rehabilitation is required. The responsiveness of the Walk-12 was not examined, nor were its properties compared to other mobility tools. However, this investigation demonstrated that the Walk-12 was a valid and reliable indicator of perceived mobility in ambulant outpatients with inflammatory PN, and is worthy of further investigation to determine its responsiveness and establish its properties in a wider range of PN.

4.4.8. Conclusion

The Walk-12 was a useful, valid and reliable measurement tool for assessment of perceived ambulatory mobility in this study. It was quick and easy to complete and includes items that assess aspects of mobility that people with PN perceive as problematic and that are not captured by other disease specific outcome tools. These aspects include running, walking long distances, concentration and the effort of walking. Interestingly, the Walk-12 was strongly associated with social functioning measured on the SF-36, indicating that it reflected some of the potential effects of mobility limitations. The Walk-12 also demonstrated internal consistency and test re-test reliability in participants. These findings show that the data yielded by the Walk-12 provide an important insight into mobility and functioning, and support its use in

people with PN. Whilst the Walk-12 was a valid indicator of perceived mobility in people with PN, there may be other mobility tools which perform equally well or better, and so future studies could compare the performance of the Walk-12 to other mobility tools. Further work is also necessary to examine the properties of the Walk-12 in inpatient and community settings, in a wider range of PN and to determine its responsiveness. Future studies could also seek to develop a new tool based on the mobility problems reported by people with PN. Items could be generated from qualitative enquiry and patient involvement to ensure that the most relevant and pertinent aspects of mobility for people with PN are captured comprehensively.

4.5. Investigation of the properties of the original and modified physiological cost index of walking in healthy and peripheral neuropathy participants

4.5.1. Background

Gait abnormalities can result in elevated energy expenditure when walking and affect the ability of individuals to function in the community (Boyd et al. 1999). Common impairments experienced by people with PN can make walking more effortful (Forsberg et al. 2004; Mueller et al. 1994) and the scores obtained on the Walk-12 from participants in Study One indicated that an increased feeling of effort negatively affected their perceived walking ability (Page 134). Therefore, as measurement of the energy used when walking is likely to be important when assessing functioning in people with PN, a valid, reliable and responsive tool is required.

The physiological cost index (PCI) was originally devised by MacGregor (MacGregor 1979) to indicate the energy expenditure (Tofts et al. 1998) or energy cost or effort of walking (Taylor et al. 1999). It was based upon the assumption that oxygen consumption and heart rate have a linear relationship at submaximal levels (McArdle et al. 1996). Thus the energy cost of walking can be indicated by measuring the change in heart rate whilst walking and walking speed (MacGregor 1979). An individual's PCI in beats per metre is calculated using the following equation:

$$\text{PCI (Beats m}^{-1}\text{)} = \frac{\text{Working HR} - \text{Resting HR (Beats min}^{-1}\text{)}}{\text{Walking Speed (Metres min}^{-1}\text{)}}$$

(MacGregor 1979)

PCI= physiological cost index, HR=heart rate

Values from healthy individuals range from 0.11 to 0.55 beats m⁻¹, with a higher value indicating greater energy cost (MacGregor 1979).

Minimal equipment is used to administer the PCI; consequently it has been proposed as a practical, low-cost, low technology alternative to cumbersome and expensive gas and calorimetric analysis equipment, which may not be available in clinical settings (Harvey et al. 1998).

Two criteria must be fulfilled in order to assess the PCI accurately. Firstly, a steady state heart rate should be reached during both the resting and walking period (Nene 1993). This is usually attained within four minutes, providing noise and distractions are minimised (Corry et al. 1996; Ijzerman and Nene 2002). Secondly, participants must walk at their usual, comfortable pace whilst the components of the PCI are measured (MacGregor 1979; Rose et al. 1991). This preferred pace of walking has been found to be surprisingly reproducible on level surfaces (MacGregor 1979).

4.5.2. Properties of the PCI

The PCI has been previously used in healthy people, amputees and spinal cord injured patients to describe and evaluate the effects of assistive equipment and interventions, including exercise, upon the energy demands of walking (Bowen et al. 1998; Boyd et al. 1999; BurrIDGE and McLellan 2000; Harvey et al. 1998; Hood et al. 2002; Ijzerman et al. 1999; Macko et al. 1997; Rose et al. 1991; Taylor et al. 1999; Tofts et al. 1998). However, no studies have used the PCI in people with PN.

Validity

The energy cost of walking (EO_2 , $\text{ml kg}^{-1} \text{m}^{-1}$) is a standard, criterion measure of the energy used while walking and has been used to evaluate the validity of the PCI by others (Bowen et al. 1998; Boyd et al. 1999; Ijzerman and Nene 2002). Values of EO_2 are calculated from oxygen consumption (VO_2) using :

$$EO_2 (\text{ml kg}^{-1}\text{metre}^{-1}) = \frac{\text{Oxygen consumption, } VO_2(\text{ml kg}^{-1}\text{min}^{-1})}{\text{Walking Speed (Metres min}^{-1})}$$

Oxygen consumption is measured whilst walking using portable indirect calorimetric systems. One system, the Metamax (Cortex, Metamax 3B, Biophysik, Leipzig, Germany) is lightweight, comfortable and provides real time readings of heart rate and VO_2 via telemetry. The validity and reliability of this system to measure VO_2 at heart rates analogous to those attained when walking is presented in Appendix Four.

Despite widespread use in a range of patient groups, the validity of PCI scores to indicate the energy cost of walking has not been widely investigated. The PCI could be valid in PN as common impairments which produce difficulties in walking increase energy demands that should be measured by the PCI (MacGregor, 1979). However, the validity could be dependent upon the patient group it is used in. Minimal association between PCI and EO_2 has been reported in 20 healthy participants and 17 people with mid thoracic spinal cord injury ($r=0.2$) (Hood et al. 2002). Others have reported moderate correlations in small studies of children with cerebral palsy ($r=0.5$; $n=17$) (Bowen et al. 1998; Ijzerman et al. 1999). Bowen et al. (1998) also reported PCI scores could not discriminate between five healthy and five children with cerebral palsy, implying poor divergent validity, although this could equally be an artefact of the small sample size. Nonetheless, these findings suggest that the validity of the PCI cannot be assumed for people with PN.

The validity and reliability of the PCI relies upon a preferred walking speed being attained consistently throughout the test. In a clinical environment, participants are likely to walk around a track of known distance. However, the distance walked in a straight line and the numbers of changes in direction are likely to influence the pace of walking, challenging validity. Some studies have used short walking track designs of 12 metres or less (Boyd et al. 1999; BurrIDGE and McLellan 2000; Ladouceur and Barbeau 2000; Sienko Thomas et al. 1996; Taylor et al.

1999), often using several repetitions on a straight track (Burridge and McLellan 2000; Ladouceur and Barbeau 2000; Sienko Thomas et al. 1996; Taylor et al. 1999). However, a track with tight turns or arcs may prevent attainment of preferred walking pace, reducing speed and thus increasing PCI scores if heart rate remains unchanged. Other authors have used longer, straight or oval designs (Boyd et al. 1999; MacGregor 1981) but no standard track has been identified for reliable and valid measurement of the PCI.

Reliability

Several studies investigating the PCI report it has poor reliability. Large variability of repeated scores has been shown in children with cerebral palsy and healthy participants (repeated values varied by >20%) (Bowen et al. 1998; Boyd et al. 1999; Ijzerman and Nene 2002). Similarly, reduced test retest reliability meant that the smallest detectable difference exceeded 40% in people with paraplegia and healthy participants (Hood et al. 2002; Ijzerman et al. 1999) and over 60% in children with cerebral palsy (Ijzerman and Nene 2002).

This inconsistency of repeated measurements has led to doubts regarding the clinical usefulness of the PCI (Bowen et al. 1998; Boyd et al. 1999; Ijzerman and Nene 2002). Variability in resting heart rate has a significant impact on the PCI's test re-test reliability (Ijzerman et al. 1999; Ijzerman and Nene 2002) but was included in the PCI equation to correct for variation in cardiovascular fitness between individuals. However, resting heart rate could be omitted from the PCI equation to improve reliability, as working heart rate is also influenced by cardiovascular conditioning and so can reflect differences in aerobic fitness (McArdle et al. 1996). Thus a new measure, the modified PCI (mPCI) which excludes resting heart rate was also investigated in this study. The mPCI is calculated from:

$$\text{mPCI (Beats metre}^{-1}\text{)} = \frac{\text{Working HR (Beats min}^{-1}\text{)}}{\text{Walking Speed (Metres min}^{-1}\text{)}}$$

Responsiveness

Large variability in repeated measurements of the PCI will affect the estimation of responsiveness. Several studies have calculated the smallest difference required to exceed the inherent variability in repeated measurements of PCI scores, and thus indicate a true alteration in walking ability. The magnitude of change required ranges from 20% to over 80% of the original PCI score in healthy people and participants with limitations (Bailey and Ratcliffe 1995; Bowen et al. 1998; Butler et al. 1984; Hood et al. 2002; Ijzerman et al. 1999; Nene 1993). This is considered unacceptable by many (Boyd et al. 1999; Hood et al. 2002; Ijzerman et al. 1999) as changes after interventions, such as exercise, are unlikely to exceed the measurement error and so cannot be reflected by the PCI. Consequently it is important to consider the responsiveness of the PCI and mPCI in people with PN to allow judgement of its usefulness.

4.5.3. Objective

The objective of the two studies in this section was to investigate the properties of the PCI and mPCI in healthy and PN participants.

4.6. Study Two – An investigation of the inter and intra-rater reliability and validity of the original and modified physiological cost index in healthy participants when walking on two tracks.

4.6.1. Background

Few studies have investigated the reliability of the PCI and only three studies have investigated its validity, finding equivocal results (Bowen et al. 1998; Hood et al. 2002; Ijzerman et al. 1999). In addition to variations in heart rate, walking speeds can vary and affect the reliability and validity of PCI and mPCI scores in response to differing track dimensions. Despite use of the PCI in a range of environments and patient groups, no one track shape has been advocated for use. Therefore, the reliability and validity of the PCI and mPCI measurements from different track shapes requires investigation to determine their suitability.

4.6.2. Aims

The aims of this study were to:

1. investigate the inter and intra-rater reliability and validity of the physiological cost index (PCI) and modified PCI (mPCI) measurements in healthy participants.
2. establish a standardised track that participants would walk upon whilst the PCI and mPCI are measured.

4.6.3. Method

A cross-sectional design was utilised to achieve the aims of this investigation (Sim and Wright 2000). Forty healthy participants were recruited from the staff and students of King's College London from email advertisement, following local ethical approval. All gave informed consent to take part and fulfilled the criteria listed in Table 4-3.

Table 4-3 Inclusion and exclusion criteria for healthy volunteers

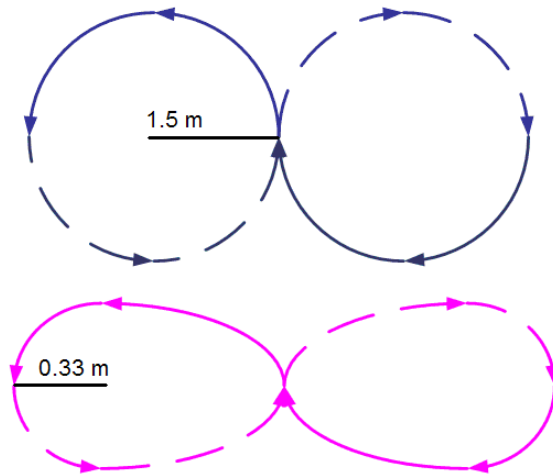
Inclusion criteria	Exclusion criteria
Ambulant	Neurological condition
Good command of the English language	Current diagnosis or a history of significant muscle, bone or joint pathology
	Respiratory disease
	Cardiovascular pathology or medication which would cause an atypical cardiac response to gentle walking
	Recent injury to lower limbs or spine

Participants were instructed to avoid eating for at least two hours prior to the test, and to wear comfortable shoes to the testing session. All measurements took place in a warm and well ventilated room.

Participants wore the Metamax system and a heart rate monitor (described in Appendix Four) and, after familiarisation, were asked to walk around two differently shaped tracks, marked on the floor, (Figure 4-2) at their normal, comfortable walking pace. The validity and reliability of the Metamax system at heart rates analogous to walking were established prior to use (Appendix Four).

One track measured 20 metres in circumference, the other 12 metres, and both had a 'figure of 8' shape. In addition to length, the main difference between the tracks was that the shorter, 12 m track had tighter turns at either end (radii were 1.5m and 0.33m for 20 m and 12 m tracks respectively) and required a period of walking in a straight line prior to each turn. The longer track line curved gradually and required minimal periods of walking in a straight line. These track designs were chosen as they were likely to fit into most clinical environments and their shape meant that an equal number of turns were made in each direction, more closely mimicking functional walking. Participants practised walking on both tracks for several minutes, whilst wearing the gas measurement system before testing.

Figure 4-2 Diagram of two tracks for PCI and mPCI measurement.



Circumferences: 20 metres for the blue track and 12 metres for the pink track. Radii of the turn on each track are shown.

Measurement of the PCI and mPCI

After familiarisation, participants sat quietly for at least four minutes and until their heart rate reached a steady state (resting heart rate, RHR). Steady state resting or working heart rate was attained when heart rate readings taken one minute apart were within five beats of each other (Bailey and Ratcliffe 1995). Once RHR was at steady state, participants began walking around a randomly assigned track at their preferred walking pace. Real time recordings of heart rate (beats min^{-1}) and VO_2 ($\text{ml kg}^{-1} \text{min}^{-1}$) were made via the telemetry system of the Metamax system throughout the resting and walking periods. Participants walked until steady state walking heart rate was reached and they had walked for at least four minutes (Corry et al. 1996; Ijzerman and Nene 2002). The time and distance walked was recorded and the participant returned to sitting. Values of speed (metres min^{-1}), energy cost (EO_2 , $\text{ml kg}^{-1} \text{m}^{-1}$), PCI (beats metre^{-1}) and mPCI (beats metre^{-1}) were calculated by one observer, after each walk.

All participants were assessed twice on both tracks by one observer (N. Smith, physiotherapy student during summer studentship) to evaluate intra-rater reliability. Thirteen volunteers were assessed a further time on each track by another observer (the author). The PCI and mPCI values between raters for this subgroup, were compared to establish inter-rater reliability. In between walks, participants sat for at least four minutes until steady state heart rate was reached before starting to walk on the next track. The order for all walks was randomised prior to commencement to eliminate order effects.

4.6.4. Analysis

The physiological cost index (PCI, beats m^{-1}) modified PCI (mPCI, beats m^{-1}) and energy cost (EO_2 $\text{ml kg}^{-1} \text{m}^{-1}$) were calculated after testing as detailed in Section 4.2.

Reliability

Reliability of the PCI and mPCI was determined in several ways (Rankin and Stokes 1998). Two way fixed intra class correlation coefficients (ICC) were calculated between PCI scores obtained by the same observer (NS) on the same track. Two way random ICC were used to examine the inter-rater reliability on both tracks (Weir 2005). The standard error of the measurement (SE_m) was also calculated for repeated measurements of the PCI and mPCI.

The smallest detectable difference (SDD) was expressed as a percentage of the mean PCI and mPCI scores for 12 and 20 metre tracks, in order to allow comparison between the two tracks.

Bland Altman plots were used to visually examine agreement throughout the range of the PCI and mPCI and 95% limits of agreement for intra and inter-rater reliability were calculated using the following formula:

$$95\% \text{ Limits of agreement} = \text{Mean}_{(x-y)} \pm 1.96 \times \text{SD}_{(x-y)}$$

where x = measurement 1 for intra-rater reliability, or the mean of measurements 1 and 2 by one rater (NS) for inter-rater reliability, y = measurement 2, or measurement 1 by a different rater (the author) (Altman and Bland 1983).

Differences between tracks

Paired t tests (two tailed, assuming unequal variance) were used to ascertain differences in PCI, mPCI, speed, EO_2 and VO_2 on each track. Differences between resting and working heart rates and VO_2 were also examined using paired t tests. A repeated measures ANOVA was used to investigate systematic differences in PCI and mPCI scores on different tracks and in the order of measurement.

Validity

To investigate the validity of the PCI and mPCI, Pearson correlation coefficients (r) were used to examine the association between PCI, mPCI and EO_2 and between change in heart rate, speed and VO_2 . Stepwise linear regression analysis was performed for the mean of PCI and mPCI scores from each track. Factors with $p < 0.05$ were included in the model and removed if $p > 0.1$.

All statistics were calculated using SPSS© software (version 11.5.1).

Significance was set at $p < 0.05$ for all tests. All values shown are presented as mean \pm standard deviation (SD) unless otherwise stated.

4.6.5. Results

40 healthy people (15 males, 25 females) were recruited. Participant variables are displayed in Table 4-4.

Table 4-4 Anthropometric data for healthy volunteers

(n=40)		Range
Age (years)	34.5 ±12.6	21-65.9
Height (m)	1.69 ±0.09	1.53-1.96
Weight (kg)	68.6 ±11.4	50-99
Leg length (m)	0.89 ±0.05	0.78-1.05

All values are mean ±SD. Leg length was measured from the anterior superior iliac spine to the medial malleolus.

The order of testing had no effect on PCI scores (repeated measures ANOVA, $p=0.28$). Oxygen consumption values were similar for both tracks and within the range validated for the Metamax in Appendix Four (Table 4-5).

Table 4-5 Scores of PCI, mPCI, VO_2 , EO_2 and components of the PCI for 20 metre and 12 metre tracks

Measure	20 metre track	12 metre track	p
PCI (beats m^{-1})	0.30 ± 0.1 (0.13-0.49)	0.34 ± 0.1 (0.14-0.6)*	<0.01
Modified PCI (beats m^{-1})	1.36 ± 0.28 (0.85–2.4)	1.53 ± 0.3 (0.98-2.5)*	<0.01
Resting HR (beats min^{-1})	72 ± 8	72 ± 9	ns
Working HR (beats min^{-1})	93 ± 11†	94 ± 12†	ns
Working VO_2 ($\text{ml kg}^{-1} \text{min}^{-1}$)	11.23 ± 2.2†	11.36 ± 2.2†	ns
Energy cost (EO_2) ($\text{ml kg}^{-1} \text{m}^{-1}$)	0.16 ± 0.02	0.18 ± 0.02*	<0.01
Speed (m min^{-1})	70.73 ±12.9	63.24 ± 11.7*	<0.01

Values are mean ±SD (range). * denotes significant difference between tracks, † denotes significant difference from resting values.

Reliability

The intra and inter-rater reliability of the mPCI was much greater than the PCI (Table 4-6). The Bland-Altman plot (Figure 4-3) shows the variation in repeated PCI scores on both tracks. The 95% limits of agreement for the mPCI indicated less variability in repeated measurements by the same and different raters when compared to the PCI (Table 4-6). The SDD was also larger for the PCI, and on the 12 metre track (Table 4-6).

Figure 4-3 Bland Altman plot of intra-rater agreement between two measurements of PCI on 20 m and 12 m tracks.

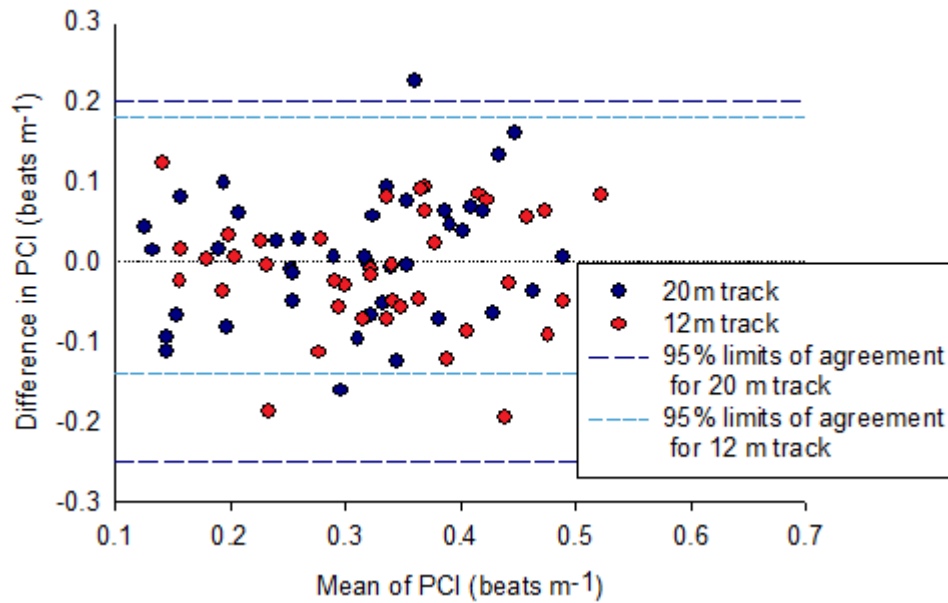


Table 4-6 Reliability of the PCI and mPCI for 20 and 12 m tracks

	PCI		mPCI	
Track	20 metre	12 metre	20 metre	12 metre
Intra-rater reliability (n=40)				
ICC	0.72	0.79	0.96	0.94
SE _m for one rater	0.16	0.21	0.16	0.21
SDD (%)	52	61	11.5	13.5
95% limits of agreement	-0.25 to 0.2	-0.14 to 0.18	-0.15 to 0.17	-0.22 to 0.19
Inter-rater reliability (n=13)				
ICC	0.76	0.85	0.81	0.74
SE _m for two raters	0.23	0.21	0.34	0.51
SDD (%)	76	63	25	33
95% limits of agreement	-0.23 to 0.18	-0.2 to 0.2	-0.3 to 0.39	-0.6 to 0.47

SE_m denotes standard error of measurement in beats m⁻¹.

Differences in PCI and mPCI between tracks

Paired t tests demonstrated that both the mean PCI and mPCI scores were significantly higher on the 12 metre track (Table 4-5). Participants also walked significantly more slowly and had a higher energy cost when walking on the 12 metre track.

Determinants of PCI and mPCI

The components used to calculate the PCI (working and resting heart rate, speed), calculated from linear regression, strongly predicted PCI ($r^2 = 0.96$ and 0.90 for 20 and 12 metre tracks respectively). Similarly, the components used to calculate the mPCI (working heart rate and speed of walking) accounted for over 90% of the variation in mPCI scores ($r^2 = 0.93$ and 0.94 for 20 and 12 metre tracks).

Validity

The assumption underpinning the PCI and mPCI that heart rate and VO_2 have a linear relationship was largely satisfied as the association between working heart rate and VO_2 was significant on both tracks (20 m: $r=0.37$; 12 m: $r=0.43$) (Cohen 1977; MacGregor 1979). There were also significant but somewhat weaker associations between working heart rate and the speed of walking on both tracks (20 m: $r=0.34$; 12 m: $r=0.33$).

The PCI and mPCI scores were significantly different when measured on different walking tracks (Table 4-5). No significant correlations between PCI and the criterion measure, EO_2 , were seen on either track (Figure 4-4) but there was a significant but weak correlation between the mPCI and EO_2 on both tracks (Figure 4-5).

Figure 4-4 Scatter plot to show relationship between energy cost and PCI

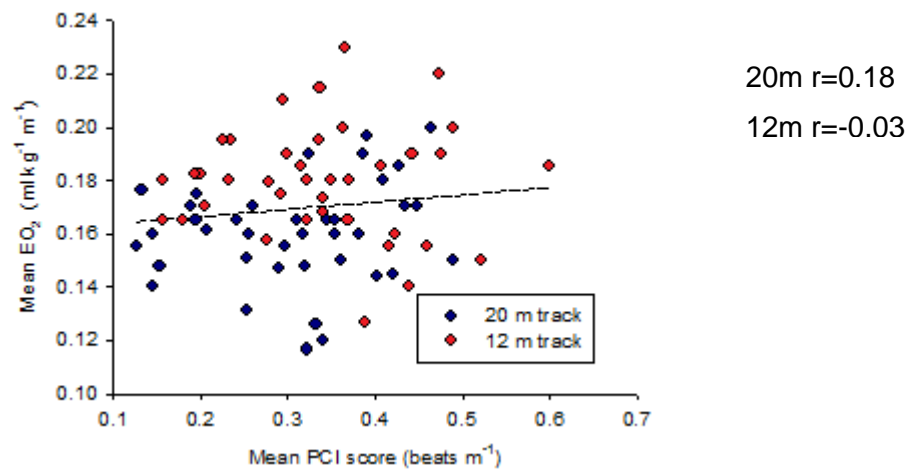
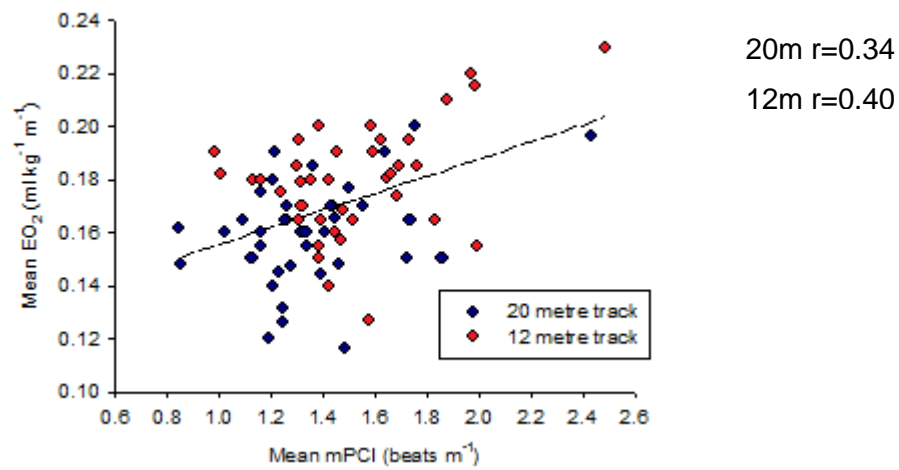


Figure 4-5 Scatter plot to show relationship between energy cost and mPCI



4.6.6. Discussion

The first aim of this study was to examine the reliability and validity of the PCI and mPCI in healthy participants when walking on two different tracks. Values for both the PCI and mPCI were higher and values for walking speed were significantly lower on the 12 metre walking track when compared to the 20 metre. These data indicated that the PCI and mPCI discriminated between the different tracks, implying divergent validity, but also showed that the track design used to measure the PCI or mPCI influenced the results.

A significant finding was that the PCI did not correlate with the standard measure of energy cost, EO_2 , on either track and repeated measurements had large variability, indicating poor criterion validity and reliability in healthy participants. The mPCI, developed and tested for the first time in this study, was more reliable and did demonstrate a significant, although not strong association with EO_2 , so was a more valid measure of the energy cost of walking in this cohort.

Reliability

In healthy participants, repeated measurements of mPCI and PCI taken by the same and by different raters on the same day were largely similar and levels of reliability were analogous to the findings of others in healthy people ($\text{ICC} = 0.74$) (Hood et al. 2002). However, despite moderate ICCs for PCI and mPCI values ($\text{ICCs} > 0.72$), there was a large variability between repeated PCI measurements. As shown in Table 4-6, a change exceeding 50% of the mean PCI score would be necessary to be sure that an alteration in PCI score was not attributable to measurement error. If the PCI was measured by two raters, an alteration in score of over 60% of the mean PCI score would be needed, although this was derived from a small sample measured by both raters ($n=13$). Others have reported similar findings in healthy participants (Hood et al., 2002). However, changes of 8% to 31% in PCI scores have been claimed to indicate a genuine alteration in walking ability in some studies (Burridge and McLellan 2000; Steven et al. 1983; Taylor et al. 1999). The results of this study suggest these interpretations are erroneous as this magnitude of change falls within the range of measurement error reported here and by others (Bowen et al. 1998; Butler et al. 1984; Hood et al. 2002; Ijzerman et al. 1999; Ijzerman and Nene 2002). Although the large measurement error seen here might not be replicated in patient groups, it is equally possible that some patient groups may demonstrate even greater variation in repeated PCI measurements. However, a limitation of this study is that serial measurements were taken on the same day, so cannot be used to judge the test re-test reliability of the PCI or mPCI over a longer and perhaps more clinically relevant period.

The reduced reliability of the PCI was primarily attributable to the variability of resting heart rate. Resting heart rate was taken after at least four minutes of rest and was at steady state. Despite these precautions, resting heart rate can vary by approximately 7% within the same participant when tested on the same day (McCrory et al. 1998). The mPCI, calculated without resting heart rate, had considerably less variability between repeated measurements which meant it had to alter by much less than the PCI to reflect a genuine change in walking (12.5%

when measured by one rater and 29% for two raters). This supports the use and further evaluation of the mPCI in future work.

Track design

The current literature does not recommend a standardised track shape or size for measurement of the PCI. The second aim of this study was to investigate two different track designs. These were selected as their dimensions were practical for most clinical environments. The results show that PCI and mPCI scores from both tracks demonstrated similar levels of validity and reliability, but it was apparent that the choice of walking track influenced PCI or mPCI scores by affecting the speed of walking. Although the PCI values from healthy participants were similar to those reported elsewhere (Bailey and Ratcliffe 1995; Ijzerman and Nene 2002; Nene 1993; Steven et al. 1983) and volunteers walked within the range of customary walking speeds (Waters and Mulroy 1999), they had significantly higher values of PCI, mPCI and EO_2 on the 12 metre track. Whilst values of PCI from the 20 metre track remained within the 99% confidence intervals calculated in MacGregor's (1979) original study (0.11-0.55), PCI scores from the 12 metre track exceeded these values. The higher values of PCI, mPCI and EO_2 were attributable to a significantly slower walking pace on the 12 metre track in the absence of a decrease in working heart rate. This appears to be an effect of the track shape. The smaller radius of turn and requirement for more turns on the 12 metre track decreased preferred walking speed. In the absence of decreased working heart rate or VO_2 , this produced higher values of PCI, mPCI and EO_2 .

This finding indicates that the same track size and shape should be used when taking serial measurements, but does not indicate one design's superiority over the other. As the 12 metre track limited walking speed, the 20 metre track would perhaps be more sensitive to improvements in walking speed brought about after rehabilitation or exercise training as it facilitated a faster preferred walking speed. Other track designs could be equally appropriate or superior to those tested here and could be investigated in future work. However, from these results, the 20 metre track is recommended for use in future work as it allowed a faster walking speed.

Validity of the PCI and mPCI as measures of the energy cost of walking. In this study, the PCI did not demonstrate validity in healthy participants as there were no significant correlations between PCI and EO_2 on either track (Figure 4-4). This is supported by the findings of others in healthy participants (Hood et al. 2002). The mPCI did demonstrate a significant, although only moderate association with EO_2 on both tracks, implying greater validity (Figure 5-6). As the only difference between the mPCI and PCI is the inclusion of resting heart rate, this finding shows that the variability in resting heart rate (discussed previously) is the likely cause of the poor association between PCI and EO_2 . Despite poor criterion validity, the PCI demonstrated divergent validity, as did the mPCI, as the scores were significantly different between 12 and 20 metre track designs (Table 4-5).

The relationship between the PCI, mPCI and $\dot{V}O_2$ is influenced by the relationship between walking speed and heart rate. In the calculation of PCI, it is assumed that walking speed and working heart rate have a co-dependent relationship. If walking speed decreased, heart rate would be expected to decrease, causing the PCI and mPCI to remain constant. In this study, the association between walking speed and working heart rate was weak ($r < 0.35$), showing this was not the case. This may be because there were a range of preferred walking speeds which were attained for a similar working heart rate in healthy people. If this is the case, changes in speed with no change in heart rate would cause variations in PCI and mPCI scores, despite no alteration in the energy used, thereby reducing their validity. Consequently, these results indicate that the PCI and mPCI are not likely to be suitable measures of the energy cost of walking in healthy participants.

However, the PCI and mPCI may have a more direct relationship with the energy cost of walking in people who have difficulty ambulating as this increases the stress on the cardiovascular system, resulting in a greater elevation of working heart rate (MacGregor 1979). Higher working heart rates will also decrease the impact of variability in resting heart rate upon PCI scores, thereby increasing the reliability of the PCI. Reports of mean walking heart rates ($144 \text{ beats min}^{-1}$) from adults with lower limb impairments (Ijzerman et al. 1999) are almost 40% greater than those seen in healthy participants in this study (93 and 94 beats min^{-1} for 20 m and 12 m tracks respectively). Therefore, the PCI and mPCI could be valid indicators of the energy cost of walking in people who have conditions which produce walking difficulties, such as PN, and still warrant investigation.

4.6.7. Conclusion

This cross sectional study demonstrated that the PCI has unacceptably large variability between repeated measurements which makes it unreliable in healthy people. The PCI scores also did not correlate with the criterion measure of energy cost (EO_2), so cannot be considered a valid indicator of energy usage in healthy people. The variability in scores were attributable to alterations in resting heart rate, therefore a new tool, the mPCI, which excludes resting heart rate was evaluated for the first time here. It had greater reliability than the PCI, with the smallest detectable difference of the mPCI required to demonstrate a change in walking ability being approximately 12% if a single rater was used (20 metre track; Table 4-6, Page 148). The mPCI also demonstrated a weak but significant association with energy cost, inferring some validity.

When participants walked on the 12 metre track they demonstrated significantly higher PCI and mPCI scores, largely as a result of reduced walking speed. Although the 12 metre track was similarly valid and reliable, the 20 metre track is preferred for measurement of the PCI and mPCI, as it allowed a faster walking pace and so would be more able to detect changes after interventions which increase walking speed.

Despite the findings of poor reliability and validity in this study, the PCI may still be a valid indicator of energy cost for some patient groups where gait abnormalities are likely to have a greater energy demand of walking than people with no gait problems. The consequent larger increases in heart rate when walking would reduce the impact of variability in resting heart rate upon PCI.

A new tool, the mPCI, developed in this study also warrants further investigation in patient groups as it was reliable and more valid than the PCI. Further work is now needed to investigate the suitability of both these tools in people with PN.

4.7. Study Three - An investigation of the reliability and validity of the original and modified physiological cost index in people with peripheral neuropathies

4.7.1. Background

In Study Two, the validity and reliability of the PCI and mPCI were examined in healthy participants on two different walking tracks and recommendations about their evaluation in people with PN were given. Despite poor reliability and validity in healthy participants, the PCI and mPCI may still be suitable for clinical populations that experience difficulty walking due to their greater energy demands which cause larger changes in heart rate. Therefore, the properties of the PCI and mPCI require investigation in people with PN.

4.7.2. Aim

The aim of this study was to investigate the test re-test reliability, validity and responsiveness of the PCI and mPCI in people with PN.

4.7.3. Method

Group One: Fourteen people with PN volunteered to participate in this cross-sectional study, (these subjects also participated in the study of fatigue displayed in Chapters Five and Six). Their data were used to determine the validity of the PCI and mPCI.

Of these 14 participants, seven participants were tested twice, one week apart to examine test re-test reliability.

Group Two: The responsiveness of the PCI and mPCI was ascertained by examining the change from the second baseline, pre-exercise measurements to values after the exercise intervention in 14 PN participants from the prospective, uncontrolled study presented in Chapter Two.

Excepting the diagnosis of a PN, all participants conformed to the inclusion criteria detailed in Table 4-3, Page 143. Ethical approval was obtained from Guy's Research Ethics Committee and participants gave informed consent.

Participants were asked to avoid caffeine for 12 hours prior to testing, not to eat two hours prior to testing and to wear comfortable clothing and shoes for each session.

The method of measurement of the PCI, mPCI and energy cost has been previously detailed (Study Two). Participants walked on the 20 m track as shown in Figure 4-2.

Energy cost (EO_2 , $\text{ml kg}^{-1} \text{m}^{-1}$), the standard measure of energy expenditure when walking, the mPCI and the PCI were calculated in Group One participants as described previously (Pages 139 and 140).

All participants completed the overall disability sum score (ODSS) (Merkies et al. 2002a), Rotterdam handicap scale (RHS), (Merkies et al. 2002b) and the SF-36 questionnaires (SF-

36) (Merkies et al. 2002c; Ware and Sherbourne 1992). These questionnaires were described in Chapter One.

4.7.4. Analysis

Data were checked for normality using Kolomogorov Smirnov tests. Parametric statistics were then used accordingly.

Validity (Group One)

Pearson correlation coefficients (r) were used to examine the association between the PCI, mPCI and the standard measure of energy cost of walking, EO_2 . Associations between heart rate, speed and VO_2 were also examined to test the assumptions underlying the PCI and mPCI in this patient group.

The divergent validity of the PCI and mPCI was examined using two tailed independent t tests, assuming unequal variance, between scores from people with PN and data from healthy participants described in Study Two.

Reliability (Group One)

The test re-test reliability of the PCI and mPCI was estimated using 95% limits of agreement (Altman and Bland 1983). The variability of repeated PCI and mPCI scores and EO_2 was examined using the standard error of measurement (SE_m), and calculating the smallest detectable difference (SDD), as shown in Study Two (Page 131).

Responsiveness (Group Two)

The standardised response mean (SRM) was calculated using changes in PCI and mPCI scores from baseline to after the exercise intervention (Chapter Two), using:

$$SRM = \frac{\text{Mean change in scores}}{\text{SD of change in scores}}$$

SRM: standardised response mean, SD: standard deviation.

Significance was set at $p < 0.05$ for all tests. All values are mean \pm SD (standard deviation) unless otherwise stated.

4.7.5. Results

All participants reached a steady state heart rate required for accurate measurement of the PCI. Participant details are shown in Table 4-7.

All values of energy consumption at rest ($4.1 \pm 1.2 \text{ ml kg}^{-1} \text{ min}^{-1}$) and when walking ($11.7 \pm 2.8 \text{ ml kg}^{-1} \text{ min}^{-1}$) were within the range previously validated for the Metamax (Appendix Four).

Table 4-7 Participant characteristics

	Validity group (n=14)	Reliability subgroup (n=7)	Responsiveness group (n=14)
Age (years)	50.7±11.5 (25-70)	50.3±6.1 (42-60)	52.4 ±13.6 (28-74)
Weight (Kg)	86.8±14.5	81.2±12.1	79.7±15.5
Height (metres)	1.74±6.7	1.73±4.3	168.4±7.6
BMI (kg m^{-2})	28.2 ±5	27.1 ±3.5	28 ±4.5
Diagnosis	6 GBS, 6 CIDP, 1 MMN, 1 PDN	3 GBS, 3 CIDP, 1 MMN	10 GBS, 4 CIDP
Overall disability sum score (0-12)	2 (0-5)	2 (0-5)	3 (0-7)
Rotterdam handicap score (9-36)	35 (22-36)	35 (30-36)	33.5 (26-36)
Physical function score from SF-36 (0-100)	75 (20-100)	75 (50-100)	70 (15-90)
PCI (beats m^{-1})	0.37 ±0.12 (0.18- 0.59)	0.36 ±0.14	0.35 ±0.13
mPCI (beats m^{-1})	1.6 ±0.42 (1.2.-2.6)†	1.46 ±0.15	1.66 ±0.6
Energy cost (EO_2) ($\text{ml kg}^{-1} \text{ m}^{-1}$)	0.19 ±0.06†	0.19 ±0.03	-
Resting heart rate (beats min^{-1})	79 ±13	79 ±12	75±15
Working heart rate (beats min^{-1})	100 ±14	100 ±14	96±15
Walking speed (m min^{-1})	62.7 ±14.2	69.2 ±12.6	61 ±11

All values are mean ±SD or mean ±SD (range) except for ODSS, RHS and SF-36 data which are median (range). † demonstrates significant differences between PN and healthy participants (from Study Two, n=40 mPCI (mean±SD)= $1.36 \pm 0.28 \text{ beats m}^{-1}$; $\text{EO}_2 = 0.16 \pm 0.02 \text{ ml kg}^{-1} \text{ m}^{-1}$).

Validity (Group One)

One participant was noted to have a very high resting steady state heart rate ($108 \text{ beats min}^{-1}$), despite normal readings of oxygen consumption ($2.9 \text{ ml kg}^{-1} \text{ min}^{-1}$). This individual's results were excluded from analysis, as the cause of this anomaly could not be ascertained.

Therefore, analysis of the validity of the PCI and mPCI was performed on data from 13 participants. Working heart rate and VO_2 were moderately and significantly correlated ($r=0.58$) but the correlation between PCI and EO_2 was weak and not statistically significant (Figure 4-6).

However, the mPCI strongly and significantly correlated with EO_2 ($r=0.87$, $p < 0.001$). This is shown in Figure 4-7.

Two participants had considerably higher values of mPCI and EO_2 as can be seen in Figure 4-7. This was likely to be because they demonstrated the slowest walking pace (45 m min^{-1} and 37.5 m min^{-1}). When these participants were excluded from analysis the correlation between mPCI and EO_2 was no longer significant ($r=0.35$, $p=0.3$).

Figure 4-6 Scatter plot to show the relationship between energy cost and PCI in PN participants ($n=13$)

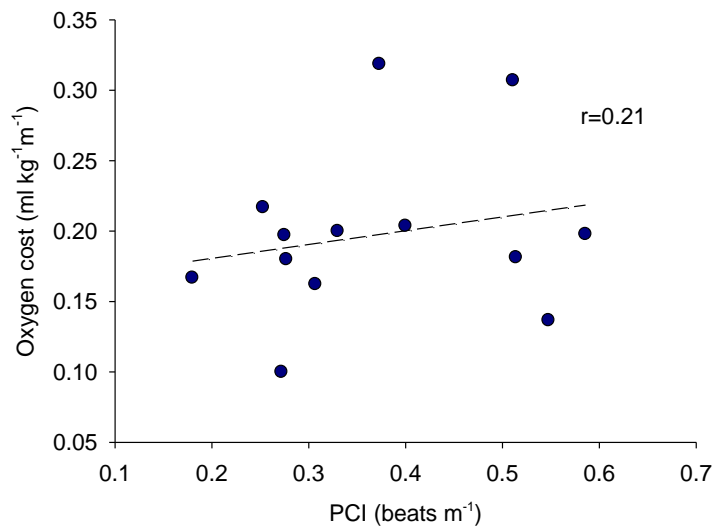
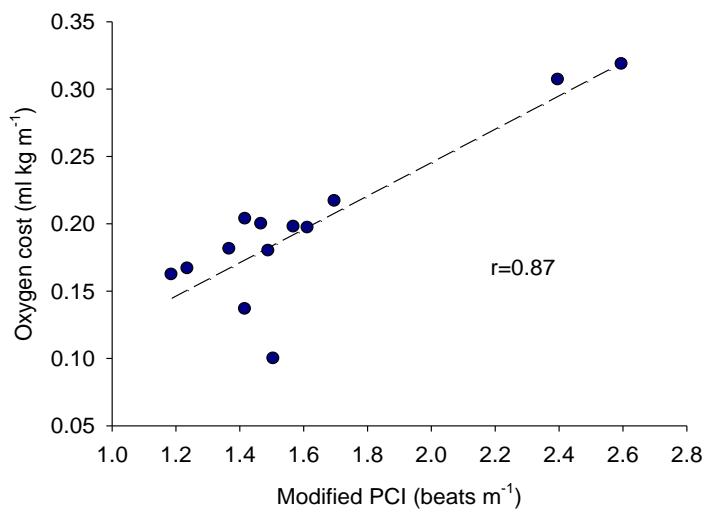


Figure 4-7 Scatter plot to show relationship between the mPCI and energy cost in PN participants ($n=13$).

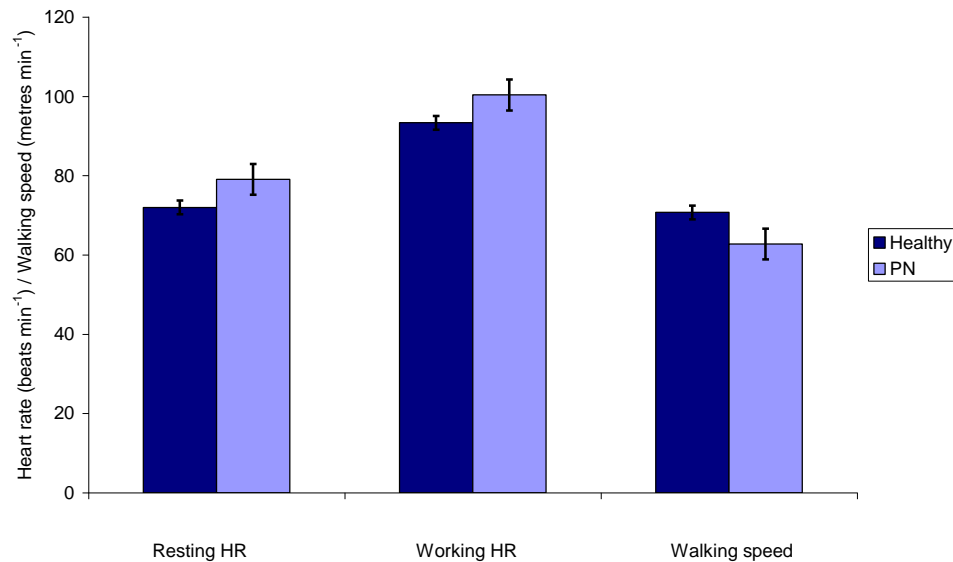


Divergent validity

Values of PCI from PN participants in this study were not statistically different to healthy data from Study Two, despite significantly higher values of EO_2 in the PN group. However, mPCI

values were significantly higher in PN participants when compared to healthy volunteers. The change in heart rate from resting to walking was the same for PN and healthy groups (21 beats min⁻¹) but PN participants exhibited somewhat higher working and resting heart rates and a slower walking pace (Figure 4-8). However, these differences did not reach significance.

Figure 4-8 Mean resting and working heart rate and walking speed for healthy and PN participants.



Error bars denote one standard error.

Reliability

Test re-test reliability was assessed on a subgroup of seven PN participants, who completed a second walk exactly one week after their initial assessment session. The values of PCI, heart rate, walking speed and EO₂ are shown in Table 4-8.

Table 4-8 PCI and mPCI scores, and walking speed and energy consumption on two occasions.

Measure	Measurement one (n=7)	Measurement two (n=7)
PCI (beats m ⁻¹)	0.36 ±0.14	0.29 ±0.08
Modified PCI (beats m ⁻¹)	1.46 ±0.15	1.5 ±0.3
Resting heart rate (beats min ⁻¹)	79 ±12	79 ±7
Working heart rate (beats min ⁻¹)	100 ±14	100 ±12
Speed of walking (m min ⁻¹)	69.2 ±12.6	68 ±16.5
Energy cost (ml kg ⁻¹ m ⁻¹)	0.19 ±0.03	0.18 ±0.05

All values are mean ±SD.

There was no significant difference between PCI scores at measurement one and two, although six people demonstrated somewhat lower PCI values at the second measurement

session. The 95% limits of agreement were large (-0.14 to 0.28) and the SE_m was 0.087 beats m^{-1} . Therefore, the smallest detectable difference for repeated PCI measurements indicated that scores would have to exceed a change of 74% of the mean PCI score ($SDD=0.24$ beats m^{-1}) to be confident of detecting a change in the energy cost of walking beyond measurement error.

The mPCI had narrower 95% limits of agreement (-0.54 to 0.46) and the SE_m was 0.19 beats m^{-1} . This indicated that a change in mPCI scores exceeding 35.5% of the mean mPCI scores was required to demonstrate a change in walking ability beyond measurement error. This was similar to the SDD of EO_2 (34%).

Responsiveness (Group Two)

The change in PCI and mPCI scores after the exercise intervention undertaken in Chapter Two was used to calculate the responsiveness of the PCI and mPCI. These changes and the SRM for both outcome tools are shown in Table 4-9.

Table 4-9 Responsiveness and change in PCI, mPCI, heart rate and walking speed.

n=14	Change after exercise	SRM
PCI (beats m^{-1})	-0.03 (-0.08 to 0.03)	0.27
mPCI (beats m^{-1})	-0.12 (0.01 to 0.24)*	0.62
Resting heart rate (beats min^{-1})	-6 (-12 to -1)	-
Working heart rate (beats min^{-1})	-3 (-8 to 3)	-
Walking speed (metres min^{-1})	4.5 (0.5 to 2.5)	-

Values are mean change (95% confidence limits). * denotes significant difference from pre exercise, baseline measurements at $p<0.05$.

As reported in Chapter Two, the PCI scores were not significantly different from baseline after the exercise intervention, but the mPCI scores were significantly improved ($p=0.04$). The responsiveness of the PCI was poor (SRM: 0.27) but the mPCI had moderate responsiveness to change (SRM: 0.62) (Cohen 1977; Smithson 2000).

4.7.6. Discussion

The PCI and mPCI were developed to indicate the energy cost of walking when indirect calorimetry systems were not available. The current study fulfilled its aims as it investigated the reliability, validity and responsiveness of the PCI and mPCI in people with PN. The range of PCI values was similar to that reported in other patient groups (0.38 to 0.4 beats m^{-1}) (Steven et al. 1983; Tofts et al. 1998). They were higher than scores in healthy people (0.11 to 0.51) (MacGregor 1981) but were generally lower than reports in people with more severe activity limitations with MS, spinal cord injuries and after stroke (0.59 to 1.3 beats m^{-1}), suggesting that the values are representative of the energy demands of walking in people with impairments (Burridge and McLellan 2000; Hood et al. 2002; Taylor et al. 1999).

Validity

Validity of the PCI

The poor association between PCI and EO_2 and the absence of a significant difference between PCI scores of healthy and PN participants in this study demonstrates that the PCI was not a valid measure of the energy demands of walking for participants with PN. Others have reported a similarly weak relationship between EO_2 and PCI in people with spinal cord injuries ($r=0.14$) (Hood et al. 2002) but a moderate, significant association between PCI and EO_2 is reported in children with cerebral palsy ($r=0.5$) and has been assumed by others who use the PCI (Bowen et al. 1998; Burridge and McLellan 2000; Tofts et al. 1998).

The PCI has been reported to be able to discriminate between the use of different walking aids and interventions in people after stroke, with arthritis and with paraplegia (Burridge and McLellan 2000; Harvey et al. 1998; Steven et al. 1983; Taylor et al. 1999) but the PCI scores in this study were not significantly different from those obtained from healthy people in Study Two, despite observed differences in heart rate and a significant difference in EO_2 . However, as median scores on the ODSS indicated only mild or moderate activity limitations, it is possible that the PCI could demonstrate validity if tested in a larger number of more affected participants. Nonetheless, the results of this study show that the PCI was not a valid indicator of the energy cost of walking in participants with PN.

Validity of the mPCI

The mPCI strongly correlated with EO_2 ($r=0.87$) demonstrating it was a valid indicator of the energy cost of walking in PN participants. Values of mPCI were significantly higher in PN participants, indicating that the mPCI also had divergent validity. These findings show that, despite the small sample, the number of participants included in the study were sufficient to allow some significant relationships to be identified. However, two participants who demonstrated considerably greater activity limitations than the majority of other volunteers (ODSS: 4 and 5) walked very slowly, producing high values of EO_2 and mPCI, thus strengthening their statistical association (Huck 2004b). When they were excluded, the correlation between EO_2 and mPCI was no longer statistically significant, although this is likely to be caused by the consequent reduction in sample size (Huck 2004b). Despite these

limitations, the results support further investigation of the mPCI in a larger and more diverse group of PN participants to establish its validity as an indicator of the energy cost of walking.

Reliability

The reliability of PCI and mPCI was examined using two measurements, recorded one week apart, in seven clinically stable PN participants.

Reliability of the PCI

The reliability of the PCI was poor, as 95% limits of agreement were large and of similar magnitude to the mean PCI score (-0.14-0.28). A non-significant reduction in PCI scores from the first to the second measurement was also observed (Table 4-6). As EO_2 differed by only 5% ($0.01 \text{ ml kg}^{-1} \text{ m}^{-1}$), the reduction in PCI scores was unlikely to be attributable to increased familiarisation with the test protocol. However, both resting and working heart rates were less variable on the second testing session, indicating a possible familiarisation effect.

The variability between repeated PCI scores indicated that scores would have to change by 74% (SDD) of the mean PCI to be confident of a change in walking ability beyond measurement error. A change of this magnitude has not been reported after intervention in any study. This provides a strong argument that the PCI is not reliable to indicate the energy cost of walking in people with PN.

Reliability of the mPCI

The mPCI was somewhat more reliable, as values varied less on repeated measurements (95% limits of agreement: -0.54-0.46). The SDD was also considerably smaller than that of the PCI (35.5% of the mean mPCI) and similar to the SDD of the standard measure of energy cost, EO_2 (34%). These findings indicate that the mPCI is less variable and thus more a reliable indicator of the energy cost of walking than the PCI in people with PN but are limited by the small sample, especially as only seven participants were used to determine the SDD. Further work is now needed to establish the reliability of the mPCI in a larger and more diverse sample and over longer, more clinically relevant time periods.

Responsiveness

After an exercise intervention (Chapter Two), PCI scores remained similar to baseline values and demonstrated poor responsiveness ($\text{SRM} = 0.27$). Although it is possible that the energy cost of walking was not improved after the intervention, decreases in heart rates and a significant increase in walking speed were observed (Table 4-9), suggesting this was not the case. Values of mPCI were significantly reduced after the intervention (by 7.5%) and demonstrated moderate responsiveness ($\text{SRM} = 0.62$) (Cohen 1977; Smithson 2000), although the improvement in mPCI scores did not exceed the SDD (35.5%). However, these findings are limited as the SDD was calculated from only seven PN participants and so cannot be applied to a wider population. Further investigation should seek to determine the SDD in a larger number of participants and to examine the responsiveness of the mPCI after exercise and after other interventions.

4.7.7. Conclusion

The assumptions underlying the PCI were met in this study as working heart rate was significantly associated with energy consumption during walking. However, this study shows that the PCI was not valid, reliable, or responsive when used in people with PN. This was primarily due to large variability in resting heart rate which was also observed in healthy participants in Study Two.

However, an alternative tool, the mPCI, calculated without resting heart rate demonstrated reliability between repeated measurements and could discriminate between healthy people in Study Two and PN participants. It also correlated with the criterion measure of energy cost in the PN group and was responsive to improvements in the energy cost of walking after a 12 week exercise intervention. These results suggest that the mPCI is a promising tool to indicate the energy cost of walking in people with PN.

However, the findings of this study are limited by the relatively small sample and lack of rater blinding which reduces their external validity. Furthermore, a disadvantage of both the mPCI and PCI is that they were designed to provide data about participants' performance in a laboratory setting and so have limited validity to usual mobility in the community. Although this could be addressed by measuring the PCI and mPCI in community settings, uncontrolled variables such as noise, distractions and other people are likely to influence heart rate, walking speed and so affect scores.

Further work is needed to confirm these findings and to establish the properties of the mPCI in a larger group of people with PN. However, these results provide some support for the use of the mPCI as a preferable measure of the energy cost of walking to the PCI in people with PN.

4.8. Chapter Discussion and Conclusion

Mobility has great importance to the individual and is a vital function for most daily activities (Chiou and Burnett 1985; Lord et al. 2004). People with PN often have difficulty with aspects of mobility, including walking, running and climbing stairs, yet there are no validated outcome tools to reflect aspects of mobility in this specific patient group (Erdmann et al. 2005; Forsberg et al. 2004). This chapter contains three studies which investigated different aspects of measurement of ambulant mobility. As each study has its own discussion and conclusion, only the main points are considered in this section. However, all three studies share some limitations which are discussed here before the results of each study are summarised.

Each study is somewhat limited by the size and nature of the sample used as all participants had to travel to London to be tested. This unintentionally excluded people with PN who had more severe activity limitations and could not access transport, thus biasing the sample. All participants were recruited as they were ambulant; this was necessary for measurement of the Walk-12, PCI and mPCI as, in their current form, these tools are not suitable for those who cannot walk. However, some people with PN are unable to walk, and so the external validity of these findings is limited. The size of the sample also limits the external validity of the findings to the PN population, particularly those studies which contained subgroups of few participants (e.g. the study of test re-test reliability in Study Three). This limitation was predominantly due to difficulties with recruiting participants who were able to re-attend for testing, and could be remedied in future studies by using multiple testing sites. Despite these limitations, the findings of these studies provide several conclusions and identify areas for further work in people with PN.

The Walk-12 mobility questionnaire appeared appropriate to use in people with PN as it demonstrated some validity, reliability and little burden with only a small floor and ceiling effect. Whilst the Walk-12 assessed aspects of self-reported mobility not questioned on other tools, it may not capture all the mobility problems experienced by people with PN and is not suitable for people who cannot walk. Further work is therefore necessary to identify and develop new tools for people with PN which can be used in non-ambulant patients, examine the properties of the Walk-12 in comparison to other tools and to establish its responsiveness. Its properties should also be evaluated in inpatients and in a broader range of PN to determine if it can be used in these groups.

A longer, 20 metre track was preferred to a 12 metre track when measuring the PCI and mPCI as it facilitated a faster preferred walking speed. However, further work could investigate if other track designs are superior. The PCI was not valid in healthy or PN participants as it did not correlate with $\dot{V}O_2$, the criterion measure of energy cost and repeated measurements were not reliable. However, the mPCI was reliable, demonstrated acceptable validity in people with PN and captured a significant change after an exercise intervention. These findings require confirmation in a larger and more diverse group of PN participants, suggest that the mPCI is a promising and appropriate tool to indicate the energy cost of walking in people with PN.

Chapter 5. An investigation of experienced fatigue in people with peripheral neuropathies

5.1. Summary

The study in this chapter investigated the feelings of fatigue experienced by people with inflammatory PN (defined as experienced fatigue) and examined potential contributors to experienced fatigue. Thirteen participants with peripheral Neuropathies (PN) and 13 healthy participants completed tools which measured experienced fatigue (Fatigue Severity Scale, FSS, Fatigue Impact Scale, FIS, and revised Piper Fatigue Scale, PFS) activity limitations (Overall Neuropathy Limitations Scale, ONLS) participation, mobility and mood. Perceived exertion during fatiguing exercise was measured using the Borg Scale. Resting heart rate, activity levels over five days and the energy cost (EO_2) of walking were also assessed.

Experienced fatigue was significantly greater for people with PN (mean \pm SD: FSS: 4 ± 1.8 ; FIS: 22.6 ± 21 ; PFS: 2.7 ± 2.1) than healthy people (FSS: 2.3 ± 0.8 ; FIS : 6.8 ± 6.9 ; PFS: 1.22 ± 1.1) on all three questionnaires and greater fatigue was significantly associated with greater activity limitations, poorer mobility and depressed mood (all $r > 0.6$). Ten PN participants noted that exercise worsened their experienced fatigue, and eight stated that severe experienced fatigue was a persistent and troublesome symptom. Participants with PN had higher resting heart rates (RHR) (mean \pm SD: PN: 79 ± 14 , H: 72 ± 8 beats per minute) and were significantly less active (activity counts over five days: PN: 1151 ± 339 ; H: 1489 ± 408 counts) than healthy controls. However, the severity of experienced fatigue was not significantly associated with heart rate or activity levels. Five out of 8 PN participants who stated that fatigue was a persistent problem did not complete the fatiguing exercise protocol and there was a general trend for PN participants to report greater perceived exertion throughout the fatiguing exercise in comparison to healthy volunteers, although this did not reach significance.

The results of this study are limited due to the small self-selected sample and the inclusion of people with a range of PN. Nevertheless, they show that participants with PN experienced significantly greater fatigue than healthy volunteers and that this was significantly associated with greater activity limitations, reduced participation, depressed mood and poorer health status. Whilst this cannot explain the mechanisms underpinning experienced fatigue, participants with PN were less fit and less active which suggest that these factors could influence the severity of experienced fatigue. Further work is now needed to confirm these results in a larger sample of people with PN, to re-examine the potential contribution of fitness, energy cost and activity levels to experienced fatigue and to consider the impact of other factors, not investigated here, which may also contribute to experienced fatigue.

This work has been presented at the World Congress in Physical Therapy 2007 and its abstract has been published:

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5.2. Background

The term fatigue is commonly used by patients and clinicians to describe feelings of tiredness, lack of energy and lassitude (Krupp and Pollina 1996). Experienced fatigue is a multi-dimensional, individual experience, and to be aware of some experienced fatigue is likely to be normal (Friedberg and Jason 1998). However, a feeling of persistent and severe experienced fatigue is a common symptom reported by people with neurological conditions, including PN, and contributes to functional limitations (Iriarte et al. 2000; Kalkman et al. 2005; Lennon et al. 1993; Lou et al. 2003; Merkies et al. 1999; Taylor et al. 2000).

Reports indicate that up to 80% (from 113) of people after GBS, with CIDP or Paraproteinaemic Demyelinating Neuropathy (PDN) complain of severe experienced fatigue several years after the onset of their neuropathy and that many consider it one of their three most limiting symptoms (Merkies et al. 1999). Severe experienced fatigue also has a negative effect upon health perception, activities and leisure pursuits in PN, and can be apparent despite otherwise good clinical recovery (Garssen et al. 2006c; Merkies et al. 1999). Little is known about the nature of fatigue experienced by people with CIDP or PDN. After GBS, experienced fatigue is independent of both the subtype of GBS and antecedent infection, but is more common in women and those over 50 years (Burrows and Cuether 1990; Garssen et al. 2006c; Merkies et al. 1999). At present the nature and mechanism behind experienced fatigue in PN are unclear and therefore it is not possible to identify interventions which may reduce its severity and functional consequences.

The second aim of this thesis was to investigate and describe the nature of fatigue in people with inflammatory PN. Experienced fatigue was investigated in the study described in this chapter whilst the physical factors which could contribute to experienced fatigue by reducing the force generating capacity of a muscle (physiological fatigue) are considered in Chapter Six (Bigland-Ritchie 1981; Gandevia 2001).

5.2.1. Operational definitions of fatigue

For clarity, operational definitions of components of fatigue used in this thesis are provided both here and on Page 41.

Experienced fatigue is defined as: “*Feelings of fatigue, tiredness, lassitude and/or lack of energy*” (Sharpe and Wilks 2002).

It is recognised that to have some experienced fatigue is likely to be normal. Severe experienced fatigue is considered to be abnormal and is defined here as: “*an excessive, abnormal feeling of tiredness or lack of energy which is not relieved by rest*” (Krupp and Pollina 1996; Piper et al. 1989).

5.2.2. Potential causes of severe experienced fatigue

Many factors may contribute to the severe experienced fatigue reported by people with inflammatory PN. These include factors that may produce physiological fatigue which are investigated in Chapter Six (Bigland-Ritchie 1981; Gandevia 2001). Likely factors considered

here were identified from the limited evidence in PN and from evidence in other neurological conditions and chronic fatigue syndrome (CFS).

5.2.3. Mood

The relationship between severe experienced fatigue and mood or well-being is likely to be complex. Severe experienced fatigue in otherwise healthy people can be caused by psychiatric disorders, most commonly depression (Skapinakis et al. 2000). Conversely, well-being could be adversely affected by severe experienced fatigue (Buchwald et al. 1997) and severe experienced fatigue is a common symptom of physical disease (Guelfi et al. 2004).

The relationship between well-being and severe experienced fatigue in PN is unclear. Garssen et al. (2004) initially reported that people with PN and severe experienced fatigue had normal levels of anxiety and depression and no other studies have examined this relationship. Their later RCT investigated the effect of anti-depressant medications upon experienced fatigue in 74 people with inflammatory PN, inferring that low mood was related to more severe fatigue (Garssen et al. 2006b). However, their finding that there was no significant difference in experienced fatigue scores between participants receiving anti-depressants or placebo indicates that this was unlikely to be the case (Garssen et al. 2006b).

In the study presented in Chapter Two, the severity of experienced fatigue, anxiety and depression was significantly improved after the exercise intervention. Garssen et al. (2004) also found that the severity of experienced fatigue was significantly reduced and anxiety and depression were significantly improved after 12 weeks of supervised aerobic training in 20 people with inflammatory PN. These findings suggest that the factors which influence experienced fatigue may also affect anxiety and depression or that they directly influence each other. Therefore, investigation of the possible relationship between anxiety, depression and experienced fatigue in people with PN is warranted.

Activity, energy expenditure and cardiovascular fitness

The findings of reduced experienced fatigue after exercise interventions in Chapter Two and the work of others (Garssen et al. 2004) indicate that the factors improved by exercise interventions may directly affect the severity of experienced fatigue. Whilst other factors, including the effect of time and attention from the investigator may be responsible for some of the observed changes in these uncontrolled cohort studies, the results in Chapter Two and Garssen et al. (2004) indicate that activity, fitness and increased energy demands may be associated with the severity of experienced fatigue in PN and require further investigation.

Physical deconditioning is thought to contribute to both severe experienced and physiological fatigue in people with CFS (Gibson et al. 1993). Some authors suggest that cardiovascular deconditioning elevates feelings of perceived exertion, and may increase the severity of experienced and physiological fatigue (Ohashi et al. 2002; Sharpe and Wilks 2002; Vercoulen et al. 1997). This is proposed to lead people with CFS to avoid exertion and activity which further reduces cardiovascular fitness and leads to greater feelings of exertion when undertaking even simple activities (Sharpe and Wilks 2002). Whilst this theory is not fully

tested and CFS has many differences from PN, it is possible that the model suggested in CFS could potentially explain the severe experienced fatigue in people with PN.

No studies have examined the relationship between general activity levels, energy use, fitness and experienced fatigue in people with PN. These factors require investigation as if they are found to be associated with experienced fatigue then targeted interventions, including exercise, could be developed to reduce experienced fatigue.

5.2.4. Aims

The aims of the study in this chapter were to:

1. describe the nature and severity of experienced fatigue in people with PN in comparison to healthy volunteers,
2. investigate the relationships between experienced fatigue, activity levels, perceived exertion, cardiovascular conditioning, activity limitations and health status in people with PN and healthy volunteers.

5.3. Method

People with a confirmed diagnosis of GBS, CIDP or PDN were recruited from the Peripheral Nerve clinic at Guy's Hospital, London to participate in this cross-sectional study. All diagnoses were secured upon standard criteria (Asbury and Cornblath 1990; Cornblath 1990; Hadden et al. 2005; Hughes et al. 2001). Healthy participants who did not complain of severe experienced fatigue were recruited via adverts from staff and students at King's College London.

A general health questionnaire, the GHQ-28, was used to screen for severe depression in all potential participants (Goldberg and Williams 1988). It is a 28 item questionnaire which measures non-psychotic psychiatric disturbance (Goldberg et al. 1997). It has demonstrated high test retest reliability (Pearson's correlation coefficients: 0.85 to 0.9) and internal consistency (Cronbach's α :0.86) in neurological conditions (Gibbons et al. 2004; Goldberg and Williams 1988). Subscale scores can be used alone or as part of the total tool (Goldberg et al. 1997). In this study the depression subscale was chosen to screen for inclusion as items were distinct from physical function, unlike other commonly used tools which measure depression. Respondents completed each item, from four possible answers, which was scored on a zero to two modified Likert scale. The maximum score of two indicates greatest severity, and a minimum score of zero represents no problem / no alteration from normal. If the score on the depression subscale exceeded zero, the individual was excluded from participation according to the exclusion criteria below.

Local ethical approval was given and all participants gave informed written consent. All participants met the criteria detailed in Table 5-1.

Table 5-1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Over 18 and under 80 years old	Electrical or metal implants e.g. pacemakers, metal joint replacements.
Good command of the English language.	Current diagnosis or treatment for muscle, nerve, bone or cardiovascular pathology or depression or other psychiatric disorder.
	Diagnosis of chronic fatigue syndrome or other known cause of fatigue.
	Pregnant or lactating women.

Before attending, all volunteers were asked if they had experienced problematic or severe fatigue in the last six months according to the definition: *“an excessive, abnormal feeling of tiredness or lack of energy which is not relieved by rest”* (Krupp and Pollina 1996; Piper et al. 1989).

If healthy people reported severe fatigue, they were excluded.

All participants were tested on two occasions one week apart. A battery of questionnaires (shown below) was completed prior to physical measurements and all testing took place in a quiet room. The order that questionnaires were given to the participant was randomised.

Table 5-2 Questionnaires used to measure experienced fatigue and other aspects of functioning

Questionnaires

Fatigue Severity Scale

Revised Piper Fatigue Scale

Fatigue Impact Scale

Hospital Anxiety and Depression Scale

SF-36

ONLS*

Rotterdam Handicap Scale*

Walk-12*

*denotes those questionnaires completed by PN participants only; all others were completed by PN and Healthy participants.

5.3.1. Assessment of experienced fatigue

Experienced fatigue was assessed using three questionnaires, the fatigue severity (FSS), fatigue impact (FIS) and revised Piper fatigue scales (PFS) (Fisk et al. 1994; Krupp et al. 1989; Piper et al. 1998). These scales were described and evaluated in Chapter One (Page 46 and 47).

5.3.2. Measurements of energy cost, cardiovascular fitness and activity levels

These tests were conducted after the questionnaires were completed.

Assessment of the energy cost of walking

The energy cost of walking ($\text{EO}_2 \text{ ml kg}^{-1} \text{ metre}^{-1}$) was measured in PN participants using indirect calorimetry, as shown in Studies Two and Three of Chapter Four (Page 139). Values of EO_2 when walking around a 20 metre figure of "8" track were compared to age and gender matched healthy data ($n=12$, 4 females, mean age: 48.5 ± 8.3 years) collected as part of a larger data set in Study Two in Chapter Four.

5.3.3. Cardiovascular fitness

Values of resting heart rate were used to indicate cardiovascular conditioning (McArdle et al. 1996). Despite intra individual variability, the resting heart rate of a group of participants is

reproducible (McCrory et al. 1997). Heart rate was measured using a heart rate monitor (Polar, Finland) in all participants after sitting quietly for at least four minutes (Corry et al. 1996; Ijzerman and Nene 2002).

5.3.4. Activity monitoring

After the first measurement session all participants were given an activity monitor (Actigraph: model AM 71624 2.2, MTI USA) to wear for one week during waking hours. The Actigraph is an uniaxial accelerometer which measures vertical displacement, weighs 43 grams, and measures accelerations from 0.05 to 2 G (G: gravitational acceleration; 1 G= 9.8 metres second⁻²), recording ten samples per second, which are summed for each minute epoch. It measures frequencies between 0.25 to 2.5 Hertz, which is the common frequency range of human movement (Warms 2006). Each displacement within these parameters is counted, recorded and stored in the Actigraph as activity counts.

Whilst direct or indirect calorimetry are considered to be the criterion method for measuring energy use (McArdle et al. 1996), the equipment required makes them impractical to use for measuring energy use outside a laboratory so they cannot provide data about usual activity levels. The MTI Actigraph activity monitor was selected to be used as, unlike questionnaires, it provides objective information regarding the intensity or frequency of movement (Warms 2006). Whilst observation of activity by a trained observer provides a large amount of data regarding activity duration, frequency and intensity, it was impractical (Warms 2006). The Actigraph is practical to wear, being worn at waist height during waking hours and only removed for bathing, although participants must remember to wear the monitors regularly. The Actigraph was preferred to a pedometer as it can only measure the steps taken and has been shown to underestimate physical activity by up to 48% (Leenders et al. 2001). Activity counts have demonstrated strong associations with double labelled water uptake ($r=0.71$), and so are a valid indicator of activity (Bouten et al. 1996). Counts from the Actigraph are strongly associated with steady state oxygen consumption and activity report in healthy people and have been used in neurological conditions, suggesting they may be appropriate for people with PN (Busse et al. 2004; Freedson et al. 1998; Munneke et al. 2001; Sirard et al. 2000; Sisto et al. 1998). Activity counts have discriminated between people with chronic fatigue syndrome and people with MS, indicating divergent validity (Vercoulen et al. 1997) and have demonstrated acceptable test re-test reliability in eight people with Parkinson's disease (ICCs >0.76) when measured one week apart (White et al. 2007b).

However, activity monitors may overestimate the energy used in low intensity activities and under estimate high intensity activities if activity counts are used to calculate energy expenditure (Warms 2006). This is because the equation used to transform activity counts to energy is inexact (Warms 2006). This suggests that values of energy expenditure should not be calculated from activity counts. However, it is reasonable to compare activity counts between groups or before and after an intervention in the same group. Therefore, the cumulative mean activity count per day over five days (counts) was collected and compared to healthy data in this study.

5.3.5. Perceived exertion

The six to 20 Borg scale was used to measure perceived exertion (Borg 1970; Borg 1982) in healthy and PN participants during fatiguing exercise which is fully described in protocol A in Chapter Six (Page 201).

Before testing, the structure of the Borg scale was explained to the participants and the verbal anchors on the scale were highlighted. Participants performed up to eight sets of ten isometric contractions of the knee extensors at 50% MVC force. Single isometric contractions were repeated at intervals during a ten minute recovery period. After each set of ten repetitions and after each single isometric contraction during the recovery period, participants were presented with a large card displaying the Borg and asked to state a number that corresponded to how hard they felt they were working at that point (Borg 1970). A higher number denoted increased perceived exertion. Participants were asked to base their response upon their overall feelings of exertion, including muscle fatigue and experienced effort (Pandolf 1982).

The Borg scale was used by participants in the exercise investigation in Chapter Two and appeared appropriate and easily understood. It is argued to have similar meaning to all participants (Dawes et al. 2005). The scale is reliable over time and is widely used to grade perceived exertion, although it has not been evaluated in PN (Borg 1970; Carton and Rhodes 1985; Cook et al. 2002; Dawes et al. 2005; Lagally and Costigan 2004). Whilst the validity of the Borg scale has been challenged in some patient groups, its widespread use, ease of application and reported reliability supported its use in this study (Sharpe et al. 2002).

5.3.6. Sample size

Many of the parameters used in this study to describe the profile of experienced fatigue have not been used in people with PN previously. However, two calculations of sample size were used to provide an indication of the number of participants required to demonstrate a significant difference to healthy participants in FSS questionnaire scores and fatigue index during a sustained MVC over 60 seconds (measured in Chapter Six).

Merkies et al. (1999) reported mean \pm SD scores on the FSS of 5.6 ± 1.4 for PN and 2.9 ± 1.1 for healthy participants. From these values, it was calculated that five participants in each group would be necessary to demonstrate a significant difference between healthy and PN groups for a power of 0.8 and significance level of 95% (two tailed).

Milner Brown et al. (1989) measured the decrease in force over an isometric 60 second contraction in 20 healthy participants and 15 people with a range of neuropathies. A fatigue index (the final force at the end of the 60 second contraction expressed as a percentage of initial force) was calculated for healthy (mean \pm SD $46\% \pm 15$) and neuropathy participants ($62\% \pm 17$). For a power of 0.8 and a significance level of 95% (two tailed) it was estimated that 16 participants in each group were necessary.

Therefore, the study aimed to recruit 16 people with inflammatory PN and an equal number of healthy participants.

5.3.7. Analysis

Fatigue questionnaires were examined using Kolmogorov Smirnov tests and frequency histograms were drawn for inspection for normality of distribution. Paired t tests (two tailed, assuming unequal variance) were used to indicate if fatigue scores changed significantly from measurement one to two.

Two tailed independent t tests were used to identify significant differences between healthy and PN groups for the mean scores on all fatigue and SF-36 questionnaires, activity counts, resting heart rate and values of EO_2 .

For the PN group, associations between the fatigue questionnaire scores, ONLS and Rotterdam handicap scale were measured using Spearman's rank correlations. Similarly, the association between anxiety and depression, SF-36 subscales, perceived exertion (total sum of Borg scores), activity counts, resting heart rate and EO_2 with fatigue questionnaire scores were examined using Pearson's correlation coefficients. The size of correlation coefficients were judged to be small/low (0.1-0.3), moderate (0.3-0.6) or large/strong (>0.6) according to published criteria (Cohen 1977).

A Kruskal-Wallis test was used to examine differences in the Borg scores of healthy and PN participants during exercise and recovery.

Differences between PN participants who complained of severe experienced fatigue (PNF), and those who did not (PNN), were examined using Mann-Whitney U tests as small numbers meant the data were not normally distributed.

Significance was set at $p < 0.05$ for all tests. All data were analysed using SPSS© software (SPSS Inc. version 11.5.1).

5.4. Results

5.4.1. Participants

Fifteen volunteers with PN conformed to the inclusion criteria and were recruited. However, one participant could not tolerate the physiological fatigue tests and one other was unable to return for the second testing visit. Therefore, 13 PN participants (four females) with PN and 13 healthy volunteers (seven females) were compared. Four PN participants had completed the exercise programme in Chapter Two at least six months prior to their participation in this study. Participant characteristics are shown in Table 5-3.

Table 5-3 Participant characteristics

	PN (n=13)	Healthy (n=13)	p
Age, years (\pm SD; range)	51.9 (\pm 11; 27.8-69.7)	44.8 (\pm 13.8; 23-65)	ns
Weight, Kg	84.4 \pm 18	73.6 \pm 16.8	ns
Height, metres	1.73 \pm 0.84	1.71 \pm 0.09	ns
BMI, Kg m ⁻²	28 \pm 5.8	25 \pm 4.7	ns
Diagnosis	GBS: 4, CIDP: 7, MMN: 1, PDN: 1		-
Mean time since diagnosis, (SD; range)	9 years, 9 months (\pm 9 months; 1 year-29 years)		-
SF-36 PCS	42.4 \pm 9.6	57.5 \pm 3.2*	<0.001
SF-36 MCS	57.6 \pm 5.3	54.4 \pm 4	ns
Walking Scale (Walk-12)	32 (\pm 21)	-	-
ONLS	4 (0-5)	-	-
Rotterdam Handicap scale	33 (22-36)	-	-
HADS Anxiety	2.5 (0-8)	-	-
HADS Depression	1.5 (0-8)	-	-

All GBS had AIDP, all CIDP participants had the typical form.* denotes significant difference between healthy and PN groups. All values are mean \pm SD except the ONLS, RHS and HADS which are median (range). SF-36 PCS – Physical component summary score, MCS – mental component summary score, HADS – Hospital anxiety and depression scale.

5.4.2. Fatigue report

Fatigue questionnaire scores were normally distributed in healthy and PN groups (Kolmogorov-Smirnov test, $p=0.2$) thus parametric statistical tests were used. There were no significant differences within groups between scores on the first and second visit for all fatigue scales. Therefore, the mean of fatigue questionnaires scores from both visits were used for all comparisons.

Mean fatigue scores for each questionnaire are shown in Table 5-4. Overall scores on the PFS were classed as mild for both groups, but affective and sensory subscales indicated moderate

fatigue in PN participants (Piper et al. 1998). Healthy fatigue scores were all within normal limits.

Participants with PN had significantly more severe experienced fatigue than healthy volunteers on the PFS, FIS and FSS. Physical and behavioural subscale scores on the FIS were also significantly higher in PN participants, indicating greater experienced fatigue.

Table 5-4 Fatigue questionnaire scores for PN and healthy participants.

Measure	PN	Range	Healthy	Range	p
FSS Total	4 ±1.8	1-6.4	2.3 ±0.8	1-4.1*	0.005
FIS Total	22.6 ±21.6	0.5-72	6.8 ±6.9	0-20*	0.02
PFS Total	2.7 ±2.1	0-6.2	1.22 ±1.1	0-3.2*	0.04
FIS cognitive	3.7 ±4	0-12.5	2.5 ±2.9	0-8	ns
FIS physical	10.3 ±8.6	0-25	1.23 ±1.6	0-5*	0.001
FIS social	10.8 ±12	0-36.5	3.2 ±3.2	0-11*	0.04
PFS behavioural	2.3 ±2.6	0-6.8	0.26 ±0.4	0-1*	0.01
PFS affective	3.8 ±2.4	0-7.1	1.84 ±1.8	0-4.8*	0.03
PFS sensory	3.3 ±2.4	0-6.6	2.1 ±1.9	0-5.2	ns
PFS cognitive	1.83 ±1.6	0-4.8	1.6 ±1.1	0-4	ns

* denotes significant difference between healthy and PN participants. All scores are mean ±SD. FSS - fatigue severity scale, FIS – fatigue impact scale, PFS – Piper fatigue scale.

In the PN group, fatigue severity was not correlated with age ($r < 0.3$), and females had similar, or slightly lower scores on the FSS (2.8 ± 2), FIS (22.6 ± 33) and PFS (1.7 ± 3) than men (FSS: 4.55 ± 1.5 ; FIS: 22.6 ± 17 ; PFS: 3.2 ± 1.6).

Participants with CIDP demonstrated significantly more severe experienced fatigue than those after GBS. Overall fatigue scores for people with CIDP and after GBS are shown in Table 5-5.

Table 5-5 Fatigue questionnaire scores of participants with GBS and CIDP.

	GBS (n=4)	CIDP (n=7)	p
FSS Total	1.7 (1.2-3.9)	5 (3.7-5.9)*	0.01
FIS Total	3.5 (0.5-20)	27 (5-72)*	0.05
PFS Total	0.5 (0-2)	4 (0.3-6)*	0.003

* denotes significant difference between people after GBS and with CIDP. All values are median (range).

On the FSS, seven PN participants rated fatigue to be one of their three most disabling symptoms and ten noted that exercise exacerbated their experienced fatigue.

Scores on all fatigue scales correlated strongly and significantly with each other in PN participants ($r > 0.7$) but there were no significant associations between fatigue scales for healthy volunteers ($r < 0.3$).

5.4.3. Experienced fatigue

In the PN group, eight participants reported that severe experienced fatigue was a significant and consistent problem during at least the last six months (PNF). The remainder of PN participants did not report persistent severe fatigue (PNN). No healthy volunteers reported severe experienced fatigue.

When compared, PNF participants displayed significantly higher scores on all fatigue scales, including cognitive subscales. These are shown in Table 5-7, overleaf.

The PN participants who reported severe persistent fatigue were slightly younger than those that did not, and reported significantly lower energy and vitality, reduced social functioning and poorer general health perception on the SF-36 questionnaire (Table 5-8). Although not statistically significant, PNF participants had higher activity limitations, measured by the ONLS.

5.4.4. Associations between experienced fatigue report, activity limitations and mental health in PN participants

Activity limitation, measured on the ONLS, mobility and depression scores were positively and significantly associated with experienced fatigue measured by the FIS and PFS in people with PN. These associations and those with the HADS and RHS are shown in Table 5-6 .

Table 5-6 Associations between activity limitations, participation, mobility and experienced fatigue.

	FSS	FIS	PFS
ONLS	0.5	0.66*	0.69*
RHS	0.34	0.43	0.3
Walk-12	0.52	0.8*	0.73*
HADS Anxiety	0.47	0.51	0.42
HADS Depression	0.7*	0.9*	0.8*

All correlations are Spearman's ranks except those between the fatigue scales and the Walk-12, which were analysed using Pearson's correlation. * denotes a significant correlation at $p < 0.05$.

The association between scores on the fatigue scales and SF-36 questionnaire for PN participants are displayed in Table 5-8. The severity of reported experienced fatigue correlated most strongly and negatively with the energy and vitality and social function subscales on the SF-36. Pain, physical function and general health perception were also significantly and negatively associated with the severity of experienced fatigue.

Table 5-7 Participant characteristics, fatigue report and other questionnaire scores for PNN and PNF participants.

	PNN (n=5)	PNF (n=8)	P
Age (years)	57 (49-70)	49 (28-62)	-
BMI (Kg m ⁻²)	31 (21-40)	26 (23-34)	-
Diagnosis	3 GBS, 2 CIDP	5 CIDP, 1 PDN, 1 GBS, 1 MMN	-
FSS	2.7 (1-5.1)	4.6 (1.9-6.3)*	0.05
FIS Total	8.2 (0-17)	29.5 (0-76)*	0.01
PFS Total	1.2 (0-2.3)	3.6 (0.2-6)*	0.007
FIS cognitive	0.4 (0-1)	6 (0-15)*	0.006
FIS physical	4.8 (0-11)	15 (0-24)*	0.05
FIS social	3 (0-7)	16.9 (0-41)*	0.02
PFS behavioural	0.26 (0-1.2)	3.9 (0-7.5)*	0.01
PFS affective	2.1 (0-4.4)	4.6 (0.2-7)*	0.02
PFS sensory	1.7 (0-3.8)	3.9 (0-6)*	0.02
PFS cognitive	0.83 (0-2)	2.7 (0-4.5)*	0.03
ONLS	2 (1-4)	4 (0-5)	ns
HADS Anxiety	1 (0-5)	3 (0-8)	ns
HADS depression	1 (0-1)	2 (0-8)	ns
Rotterdam handicap scale	33 (26-36)	33.5 (22-36)	ns
SF-36:			
Physical function	66 ±19	62 ±25	ns
Role limitation physical	80 ±4.7	68 ±40	ns
Role limitation mental	100 ±0	100 ±0	-
Social function	95.6 ±10	81 ±15	0.07
Mental health	90.4 ±4.6	79.4 ±14	ns
Pain	77.8 ±11	60 ±23	ns
Energy and vitality	79 ±16	44.3 ±16*	0.006
General health perception	80 ±9	45 ±16.3*	0.001
Walking scale (Walk-12)	24 ±5	37 ±26	ns

* denotes significant difference between PN participants who reported severe experienced fatigue (PNF) and those who did not (PNN). All values are median (range) except SF-36 summary and subscale scores and Walk-12 scores which are mean ±SD.

Table 5-8 Associations between SF-36 subscales and fatigue questionnaires for PN participants.

	FSS	FIS	PFS	FIS physical	FIS cognitive	FIS social	PFS behavioural	PFS Affective	PFS Sensory	PFS Cognitive and mood
SF-36 Physical function	0.4	0.6*	0.45	0.5	0.6*	0.66*	0.58	0.45	0.39	0.37
SF-36 Social function	0.67*	0.9*	0.72*	0.86*	0.76*	0.91*	0.84*	0.63*	0.63*	0.63*
SF-36 Mental health	0.44	0.78*	0.59	0.77*	0.76*	0.74*	0.57	0.55	0.4	0.7*
Sf-36 energy and vitality	0.86*	0.82*	0.9*	0.88*	0.77*	0.76*	0.82*	0.86*	0.88*	0.3*
SF-36 Pain	0.5	0.77*	0.71*	0.72*	0.6*	0.68*	0.71*	0.6*	0.66*	0.72*
SF-36 General health perception	0.56	0.62*	0.68*	0.75*	0.53	0.65*	0.52	0.63*	0.5	0.54

* denotes a significant association at $p < 0.05$. All values are Pearson's correlation coefficients and were negative (i.e. increased fatigue scores were associated with poorer health status on the SF-36) There were no significant associations between any fatigue scale and physical role limitation, mental role limitation, or change in health subscales (data not shown).

5.4.5. Energy demands of walking

One PN participant was uncomfortable whilst wearing the face mask used to measure EO_2 , therefore the oxygen cost of walking was examined in 12 PN participants. These data were compared to values from 12 healthy gender and age matched participants from Chapter Four. Participant characteristics and values of EO_2 are shown in Table 5-9.

There was no significant difference in the energy cost of walking between PN and healthy participants (Table 5-9). However, as people with PN were significantly heavier than healthy, age and gender matched participants, EO_2 was also calculated excluding body weight from:

$$\text{EO}_2(\text{ml m}^{-1}) = \frac{\text{Oxygen Consumption (VO}_2 \text{ ml min}^{-1})}{\text{Walking Speed (metres min}^{-1})}$$

This revealed that PN participants used significantly more energy whilst walking than healthy participants (Table 5-9).

Table 5-9 Healthy and PN participant characteristics for the energy cost of walking.

	Healthy (n=12)	PN (n=12)	P
Age, years	48.5 ±8.3	52.1 (11.5)	ns
Height (metres)	1.66 ±0.09	1.73 ±0.9	ns
Weight (Kg)	68.9 ±11.5	84.4 ±18*	0.01
BMI (Kg m ⁻²)	25 ±3.2	28.4 ±6.4	ns
Normalised EO_2 (ml kg ⁻¹ min ⁻¹)	0.16 ±0.02	0.19 ±0.05	ns
EO_2 (ml ⁻¹ m ⁻¹)	11.1 ±2.3	16.5 ±7*	0.02
Resting heart rate (beats min ⁻¹)	72 ±8	79 ±14 [#]	0.04
Activity levels (counts)	1489 ±408	1151 ±339*	0.03

*denotes significant difference between healthy and PN groups. [#] denotes n=11 resting heart rate measurements in the PN group as one PN participant's heart rate readings were faulty. All are expressed as mean ±SD. Healthy data are from 12 age matched participants who participated in a previous study (described in Chapter Four).

There were no significant differences in EO_2 (normalised to body weight) between PNF and PNN participants (Table 5-10) although the size of each group was small.

Table 5-10 Differences in EO_2 , resting heart rate and activity in PNF and PNN participants

	PNF (n=8)	PNN (n=4)	P
Normalised EO_2 (ml kg ⁻¹ min ⁻¹)	0.21 ±0.07	0.18 ±0.04	ns
Resting heart rate (beats min ⁻¹)	78 ±11	72 ±9 [#]	ns
Activity levels (counts)	1132 ±340	1181 ±375	ns

[#] n=3 as readings of one PNN participant's resting heart rate were faulty so was excluded from comparison.

Values of EO_2 were not significantly correlated with fatigue scores on any of the questionnaires in PN participants ($r < 0.3$).

5.4.6. Resting heart rate

The mean resting heart rate of PN participants was significantly higher than age matched healthy people (Table 5-9). The PNF group also had somewhat higher resting heart rates than PNN groups, but the difference was not significant (Table 5-10). Resting heart rate was not significantly associated with experienced fatigue measured on the FSS, FIS and PFS questionnaires for PN participants ($r < 0.1$).

5.4.7. Activity counts

Activity counts for PN and healthy participants are shown in Table 5-9 and for PNF and PNN participants in Table 5-10. Participants with PN had significantly lower activity counts over five days than healthy volunteers. There were no significant differences in activity levels between PNF and PNN participants.

The mean activity counts of PN participants did not significantly or strongly correlate with scores on the FSS and PFS questionnaires ($r < 0.3$), but had a moderate, positive association which reached significance with scores on the FIS ($r = 0.56$, $p = 0.048$). In healthy people, there were no significant associations between scores on the fatigue questionnaires and activity levels.

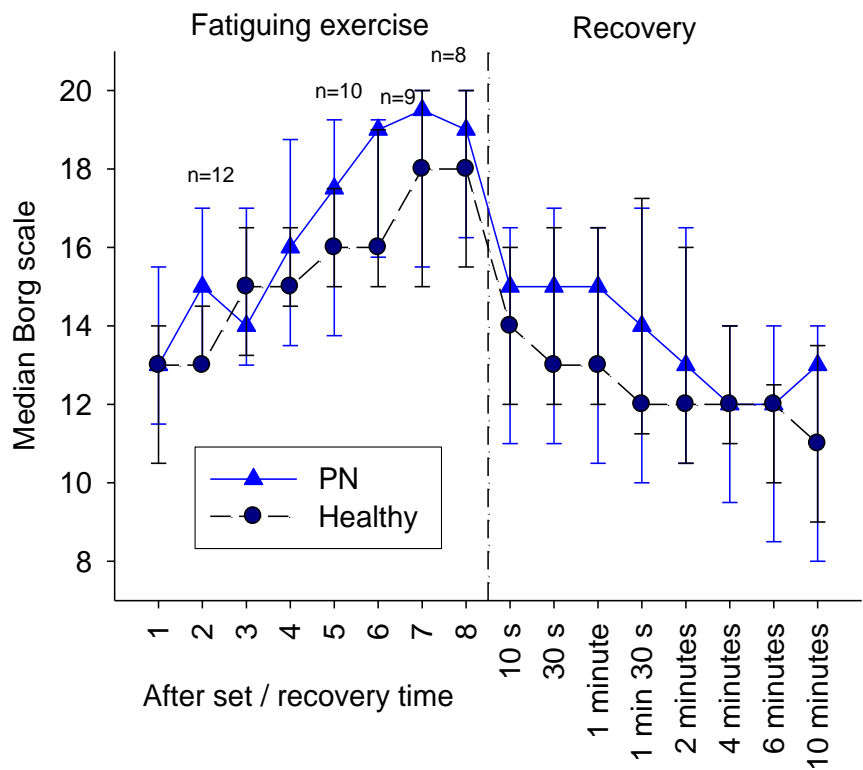
5.4.8. Perceived exertion during fatiguing contractions

Borg scores for healthy and PN participants are displayed in Figure 5-1.

Participants with PN had slightly increased feelings of exertion earlier in the fatigue protocol when compared to healthy people, but differences were not statistically significant. They recovered slightly more slowly. Five PNF participants stopped the fatigue protocol; three as they reported they were too tired to continue, and two as they were unable to continue to produce adequate force (as shown in Chapter Six). All PN participants who did not complete all repetitions were assumed to have a maximum Borg score (20) after the point at which they stopped.

There were no significant differences in perceived exertion between PNF and PNN participants. The sum of all Borg scores during the fatiguing exercise did not correlate with scores on any fatigue questionnaires in PN or healthy participants ($r < 0.5$). It also did not have any significant associations with EO_2 or resting heart rate ($r < 0.5$).

Figure 5-1 Median scores of perceived exertion during 80 intermittent voluntary contractions at 50% MVC and during recovery for healthy and PN participants.



Error bars denote 25th and 75th centiles for the median Borg score. The size of the PN group as the fatigue protocol progresses is also shown, as five PNF participants did not complete the entire protocol. All participants in both groups (n=13) completed the recovery contractions. There were no significant differences between PN and healthy groups.

5.5. Discussion

The aim of this study was to describe the nature and severity of experienced fatigue in people with PN in comparison to healthy volunteers and investigate the relationships between experienced fatigue and selected aspects of functioning. This is the first investigation of the relationship between activity levels, fitness, perceived exertion, anxiety, depression and experienced fatigue in people with PN and demonstrated that PN participants experienced significantly more severe fatigue than healthy volunteers. Whilst the findings of this study cannot elucidate the causes of experienced fatigue and its effect upon aspects of functioning in people with PN, the severity of experienced fatigue was significantly associated with decreased social function, lower mood, poorer general health perception, reduced activity levels and poorer perceived mobility (all $r > 0.6$). When compared to healthy, age matched volunteers, people with PN had significantly higher resting heart rates, weighed more and were less active. Ten (from 13) PN participants noted that exercise increased the severity of their experienced fatigue.

5.5.1. Description of experienced fatigue

This study showed that severe experienced fatigue was significantly and moderately associated with persistent activity limitations and reduced health related functioning ($r > 0.6$ for all correlations). This has been reported by others in PN (Merkies et al. 1999). The scores on the fatigue questionnaires indicated that PN participants found that experienced fatigue had the greatest impact upon social and physical activities. Contrary to the findings of Garssen et al (2006), the severity of experienced fatigue was similar between men and women, was not increased with age and was somewhat greater in participants with CIDP when compared to those after GBS, although this may be an artefact of the sample size and composition.

5.5.2. Possible contributors to experienced fatigue

Mood

Poorer mood and well-being, measured on the HADS and SF-36 were significantly associated with increased experienced fatigue in PN participants (all $r > 0.7$) which is supported by the findings of others in people after GBS and with CIDP (Merkies et al. 1999). In the current study, fatigue and depression scores measured on the HADS had a significant and strong association with each other ($r > 0.7$). This could suggest that more severe experienced fatigue was a symptom of depression or alternatively, that it precipitated feelings of low mood. Psychological factors and experienced fatigue have been shown to be linked in other neurological patient groups including MS (Iriarte et al. 2000; Strober and Arnett 2005), although not by others in PN (Garssen et al. 2004) and anti-depressants were ineffective in reducing the severity of fatigue in people with PN (Garssen et al. 2006b). It seems most likely that, as all participants were screened to exclude severe depression (using the GHQ-28), and did not demonstrate abnormal depression scores on the HADS, the significant and strong association between depression and fatigue scores could be because they share some common symptoms. However, the findings of this study are limited as only anxiety and

depression were specifically examined. Other factors which may influence both well-being and experienced fatigue such as sleep disturbances and beliefs about fatigue, not investigated here, could be responsible and should be examined in future work to determine any associations with experienced fatigue in people with PN.

Activity levels, perceived exertion, energy cost and cardiovascular fitness
Cumulative activity levels were significantly lower in PN participants than healthy volunteers and were moderately and significantly associated with severity of experienced fatigue on one questionnaire ($r=-0.56$). However, this study cannot identify if people with PN have reduced their activity levels because of an increased severity of fatigue or if reduced activity has precipitated increased experienced fatigue.

People with PN had significantly higher resting heart rates than age and gender matched healthy volunteers and those PN participants that reported persistent severe fatigue (PNF, $n=8$) had somewhat higher resting heart rates than those who did not (PNN) (PNF mean resting heart rate: 78 ± 11 beats min^{-1} ; PNN: 72 ± 9 beats min^{-1}). Despite significant differences in resting heart rate and experienced fatigue between healthy and PN groups, resting heart rate and experienced fatigue were not associated in people with PN ($r<0.1$) which suggests that cardiovascular fitness did not influence fatigue in participants with PN. However, although heart rate is commonly used and valid to indicate cardiovascular conditioning, it is not as sensitive as other tools such as peak oxygen consumption (VO_2 max) recorded during exercise (McArdle et al. 1996). Heart rate also varies at rest (as shown in Study Two of Chapter Four), which might reduce the size of any statistical association. The small sample may have also limited the strength and significance of associations and so cardiovascular fitness cannot be confidently excluded as a potential contributor to the severity of experienced fatigue.

Similarly, associations between EO_2 and the severity of experienced fatigue were weak and not significant ($r<0.3$) and there were no significant differences in normalised EO_2 between participants with PN and age and gender matched healthy participants. This is in contrast to the findings of a small study of 14 people with post polio syndrome (Brehm et al. 2006) who found that people with post polio syndrome used significantly more energy when walking than healthy participants, and that the energy cost of walking was strongly and significantly associated with reduced lower limb muscle strength ($r=0.84$, $p<0.001$). Although the results of the current study suggest that an increased energy cost of walking was not a contributor to the severity of experienced fatigue, people with PN were significantly heavier than age and gender matched healthy controls which may have skewed the results. Further work is therefore needed to compare the energy cost of walking between people with PN and healthy participants who are also matched for weight.

During the fatiguing exercise test, there was a trend for PN participants to report higher levels of perceived exertion earlier than healthy volunteers, although this did not reach significance. Reduced cardiovascular fitness, and/or an increased sensitivity to exertion may be responsible for this tendency. An elevated perception of exertion may be a regulatory, learnt protective

response in people with CFS (Noakes et al. 2004; Noakes et al. 2005) and may be a mechanism to avoid overwork, limit feelings of fatigue and to allow continued functioning after exertion (Noakes et al. 2004; Noakes et al. 2005). However, avoidance of activity and exercise in this way is thought to further reduce fitness and worsen symptoms in people with CFS (Sharpe, 2002). An altered perception of exertion may also explain the failure to complete fatiguing exercise in five PN participants who complained of severe fatigue (PNF) due to feelings of tiredness and fatigue. Three of these five PNF participants were able to maintain the force required by the test, despite stopping the test because they were exhausted. In addition to an altered perception of exertion, early cessation of fatiguing exercise could be reinforced by an expectation of increased severity of experienced fatigue after exercise, such as that reported by ten PN participants in this study on the FSS questionnaire.

Despite trends in some measures, PN participants who complained of severe experienced fatigue (PNF group) did not demonstrate significant differences from non-fatigued PN participants (PNN) in most measures of participation and activity limitations. This is likely to be attributable to the very small size of these subgroups. There were also no significant differences between PNF and PNN groups in activity levels, the energy cost of walking and resting heart rates. However, trends of increased resting heart rate, elevated energy cost and reduced activity levels were observed in the PNF group, implying that they might contribute to more severe experienced fatigue. These findings suggest that future work should utilise a larger sample and specifically select a greater number of PN participants with severe experienced fatigue. This would allow comparison between non-fatigued and fatigued PN volunteers, to determine if the trends seen in the current study would be replicated and reach statistical significance.

Taken together, the findings from this study indicate that experienced fatigue is significantly associated with reduced participation, poorer mood, reduced activity levels and greater activity limitations. The results also suggest that reduced fitness and activity levels could contribute to, or are affected by, severe experienced fatigue in PN participants. Reported reductions in the severity of experienced fatigue and improvements in activity and fitness after exercise interventions in people with PN support this suggestion, although these changes could not be directly attributed to exercise due to the uncontrolled, unblinded designs (Garssen et al., 2004; Chapter Two).

Other contributors to experienced fatigue

As this investigation only assessed some of the possible causes of fatigue, other factors which were not considered here could contribute to the severity of experienced fatigue in people with PN. In addition to increased physiological fatigue, examined in Chapter Six, factors such as increased immune activation could also be involved in experienced fatigue in people with CIDP, as it has been associated with reported fatigue in other chronic, immune mediated neurological conditions (Iriarte, Subira, & Castro 2000). In addition, significantly lower levels of hypocretin, a neuropeptide associated with narcolepsy and excessive daytime sleepiness, have been shown in 65% of 18 GBS patients during the acute illness (Kanbayashi et al. 2002;

Nishino et al. 2003). However, this finding has not been replicated and is based on a small number of patients, and may not persist beyond the acute stage of GBS. Nonetheless, both immunoactivation and hypocretin levels could be considered in addition to examination of a range of psychological factors, sleep patterns and peak VO_2 during exercise testing for future investigations of experienced fatigue in people with PN.

5.6. Limitations

The findings of this study are limited by several factors. The target sample size of 16 participants in the PN group was not reached, reducing statistical power and external validity. Whilst this may be because potential PN participants did not perceive fatigue as an important problem, it could equally be because travel to London for testing was difficult or that the inclusion criteria and nature of the physiological fatigue tests (Chapter Six) meant potential subjects, particularly those with severe experienced fatigue, were unwilling or unable to participate. This reduces the external validity of the results, as does the relatively narrow range of PN studied. There was considerable variability in scores on several measures in the PN group which, whilst increasing external validity, made statistical significance difficult to achieve on some tests. Lack of assessor blinding may also bias measurements. This could be addressed in future work by using a blinded assessor.

The nature of experienced fatigue reported by the PN group is also likely to be influenced by the fatigue questionnaires used in this study. As they were not designed to measure fatigue in this patient group, they may be unable to fully reflect the nature and severity of experienced fatigue experienced by people with PN, restricting our understanding of their experienced fatigue. Future work could seek to develop new tools for people with PN, using patient involvement to develop items from qualitative enquiry. However, the tools selected for the current study are well used and validated in other neurological conditions and alternative methods of examining fatigue, such as qualitative enquiry, would not allow direct comparison of the nature and severity of experienced fatigue between healthy and PN participants and so would not fulfil the aims of this study.

Another limitation is that all participants were volunteers and so could be considered to have an atypical interest in fatigue. Healthy participants were screened to exclude those who stated that they experienced severe fatigue, so they may have under reported fatigue on the questionnaires to please the investigator. Conversely, PN participants who initially stated that they had severe experienced fatigue may have felt compelled to indicate more severe levels of fatigue on questionnaires. However, the levels of fatigue experienced by PN participants in this study (mean FSS score: 4; range: 1 to 6.4, where 7 = most severe fatigue) were less severe than reported by Merkies et al. (1999) and Garssen et al. (2004) levels (FSS= 5.6 to 6.1) suggesting this was not the case.

5.7. Conclusions

This is the first study to describe several aspects of the nature of experienced fatigue in people with PN. Whilst its findings are limited by aspects of the design and sample size, the results provided some important data about the nature of experienced fatigue in this patient group. Participants with PN reported a significantly greater severity of experienced fatigue than healthy volunteers. This fatigue was associated with increased activity limitations, decreased social function, poorer general health perception and poorer perceived mobility.

The results were unable to identify other clear factors which influenced the severity of experienced fatigue. However, the results suggest that a combination of factors could contribute to or be affected by, the severity of experienced fatigue. These include decreased cardiovascular fitness and reduced daily activity levels which were all significantly different to those in healthy participants. It is not known whether these factors are a result of, or play a part in increasing activity limitations and poorer health status which were significantly associated with an increased severity of experienced fatigue. It is also unclear whether these factors initiated worsened experienced fatigue or if severe experienced fatigue reduced functioning in these areas, although this could be elucidated in a future longitudinal study. Other areas not considered in this study including immune system activation, sleep disturbance and psychological factors now warrant investigation as they could contribute to experienced fatigue in people with PN.

Further work is also necessary to address the limitations of this study and to confirm the findings in a larger PN patient group to inform a targeted intervention to treat severe experienced fatigue.

Chapter 6. An investigation of physiological fatigue in people with peripheral neuropathies

6.1. Summary

Physiological factors, including poor muscle activation and reduced muscular endurance may contribute to severe experienced fatigue in people with PN and were investigated in this chapter.

The physiological fatigue profile of the knee extensors of 13 people with peripheral neuropathies (PN) (4 females; Mean age: 51 ± 2 years; Diagnosis: 7 CIDP, 4 GBS, 2 other) and 13 healthy participants (7 females; Mean age: 44.8 ± 14 years) was compared. Measurements included the voluntary activation, surface EMG, strength, response and recovery from i) Protocol A, intermittent isometric voluntary contractions (up to 80 repetitions at 50% MVC) and ii) Protocol B, a 60 second sustained isometric MVC and intermittent electrical stimulation of the knee extensors.

Apart from significant muscle weakness in people with PN (H Mean \pm SD: 7.5 ± 2.2 N Kg⁻¹ ; PN: 5.4 ± 2 N Kg⁻¹) there were no significant differences in any measurements between healthy and PN groups including voluntary activation (H: $85 \pm 10\%$; PN: $92 \pm 7\%$), changes in surface EMG, delayed low frequency recovery and force decline during a sustained contraction (H: $59 \pm 18\%$; PN: $60 \pm 14\%$). In addition, there was no significant difference between PN participants who complained of severe experienced fatigue (PNF) and those who did not (PNN).

Five of eight PNF participants were unable to complete all voluntary repetitions during protocol A. However, there were no significant differences in their voluntary activation, recovery or performance to other PN participants during Protocol B.

When these results were considered with those from Chapter Five, experienced fatigue in the PN group was not associated with any measures of physiological fatigue including reduced muscular endurance or voluntary activation. Although cardiovascular fitness and knee extensor strength were significantly reduced compared to healthy people, these factors were not significantly associated with experienced fatigue in people with PN. Therefore, further investigation of factors affecting experienced fatigue is warranted in a larger number of people with PN. Further work is also necessary to investigate physiological fatigue after more functional exercise and examine differences between diagnostic subgroups.

This work has been presented at the World Congress in Physical Therapy 2007 and its abstract has been published:

Graham, R.C., White, C.M. Experienced and muscular fatigue in people with peripheral neuropathy *Abstract Physiotherapy 2007* Vol. 93 Supplement 1, p S124

6.2. Background

People with PN often complain of severe experienced fatigue after exertion or exercise, suggesting that altered physical or physiological factors influence experienced fatigue (Garssen et al. 2004; Merkies et al. 1999).

Physiological fatigue is defined as: “*a reduction in the ability of a muscle to maintain or produce force*” (Bigland-Ritchie 1981; Gandevia 2001). It may be produced by changes in the central and peripheral nervous systems, or within the muscle itself. To experience some physiological fatigue during physical exertion is considered normal (Bigland-Ritchie 1981; Gandevia 2001), but abnormal physiological fatigue could elicit severe experienced fatigue, reduce function and limit performance if already weakened muscles further decrease their force output during or after activities.

Many people with weakened muscles may use near maximal forces to perform activities of daily living (ADLs), thus even small decrements in force could severely increase the effort required to perform simple ADLs and so hinder functioning (Milner-Brown and Miller 1989; Shumway-Cook et al. 2002). Reductions in the force generating capacity of some muscles could also require patients to perform compensatory movements to complete activities of daily living, increasing energy expenditure (Waters and Mulroy 1999), which may add to the severity of experienced fatigue and perceived exertion. Therefore, investigation of physiological fatigue is needed to determine if people with PN experience an earlier onset, greater severity or longer lasting physiological fatigue when compared to healthy volunteers.

There are a number of factors that could alter the physiological fatigue profile in people with inflammatory PN. These are discussed in more detail in Section 6.2.2 (Page 192) and include changes in voluntary activation, nerve and neuromuscular propagation and alterations in the muscle and its metabolism. These aspects have been investigated in several different patient groups, but studies in PN are inconclusive. Reduced voluntary activation and altered muscle fatigability have been shown to produce abnormal physiological fatigue in people with enlarged motor units after polio (Allen et al. 1994; Allen et al. 2004). Whilst there are clear differences between the pathophysiology of polio and PN, enlarged motor units may be present in over half of people with inflammatory PN which suggests that people with PN could also have an altered physiological fatigue profile (Dornonville de la Cour et al. 2005).

In PN, two studies reported reduced muscular endurance during a sustained isometric contraction of the knee extensors and ankle dorsiflexors in people with PN ($n=15$, 10 with PN, $n=5$ with other neuromuscular disorders) and CMT ($n=29$) when compared to healthy participants (Lindeman et al. 1999; Milner-Brown and Miller 1989). Similarly, in 15 people with neurogenic weakness including PN, the fatigability of the knee extensors was significantly greater than healthy participants and was strongly related to muscle strength ($r=-0.88$) indicating that the changes producing muscle weakness may also increase physiological fatigue (Milner-Brown and Miller 1989). In contrast, others have shown significantly greater muscular endurance of the ankle dorsiflexors in 40 people after GBS during repeated

isokinetic contractions, compared to healthy participants, despite significant weakness (Dornonville de la Cour and Jakobsen 2005). Increased muscular endurance has also been reported in the knee extensors and dorsiflexors of people with diabetic neuropathy (Andersen 1998). Whilst the reason for this is unclear, it could be because the remaining innervated muscle fibres have to work harder to compensate for overall muscle weakness during daily activities and so become more resistant to fatigue.

In addition to their contradictory findings, the clinical relevance of these studies is limited as none measured or detailed the relationship between experienced and physiological fatigue. However, two studies have investigated the association between experienced fatigue and factors which may contribute to abnormal physiological fatigue including nerve conduction velocities, muscle endurance and voluntary activation in people after GBS or with CIDP (Garssen et al. 2005b; Garssen et al. 2006a). One study found narrower nerve conduction velocity distributions in 15 people with PN (GBS: n=13, CIDP n=2) who complained of severe experienced fatigue in comparison to healthy controls, but conduction velocities were not significantly associated with the severity of experienced fatigue (Garssen et al. 2006a). In the second study, physiological fatigue during a sustained MVC of the biceps brachii in 10 people after GBS did correlate significantly with experienced fatigue ($r=0.66$, $p=0.04$), but was not different to healthy participants (Garssen et al. 2005b). Whilst methodological differences, such as the muscle tested and the method of fatiguing it may account for these somewhat conflicting results, they indicate that further investigation of physiological and experienced fatigue is needed to determine if there is a relationship between them in people with PN.

A limitation of several studies of fatigue is that they have reduced relevance to everyday function as they utilised sustained contractions to elicit physiological fatigue. This type of contraction is not as common as a sub-maximal intermittent contraction when undertaking activities of daily living such as climbing stairs and walking (Garssen et al. 2005b; Lindeman et al. 1999; Milner-Brown et al. 1986). Furthermore, upper limb or smaller muscles were often tested despite the fatigue profile of these muscles being likely to have a very limited impact upon daily performance or experienced fatigue when compared to larger weight bearing muscles, such as those used when walking. Weakness brought about by abnormal physiological fatigue in these muscles could influence the severity of experienced fatigue as individuals have to work harder and utilise compensations which necessitate greater energy and effort (Gandevia 2001). Therefore, measurement of physiological fatigue in larger and weight bearing muscles during more functional muscle activity is warranted in order to mimic physiological fatigue during everyday activities and investigate any associations with experienced fatigue.

6.2.1. Aims

The aims of this study were to:

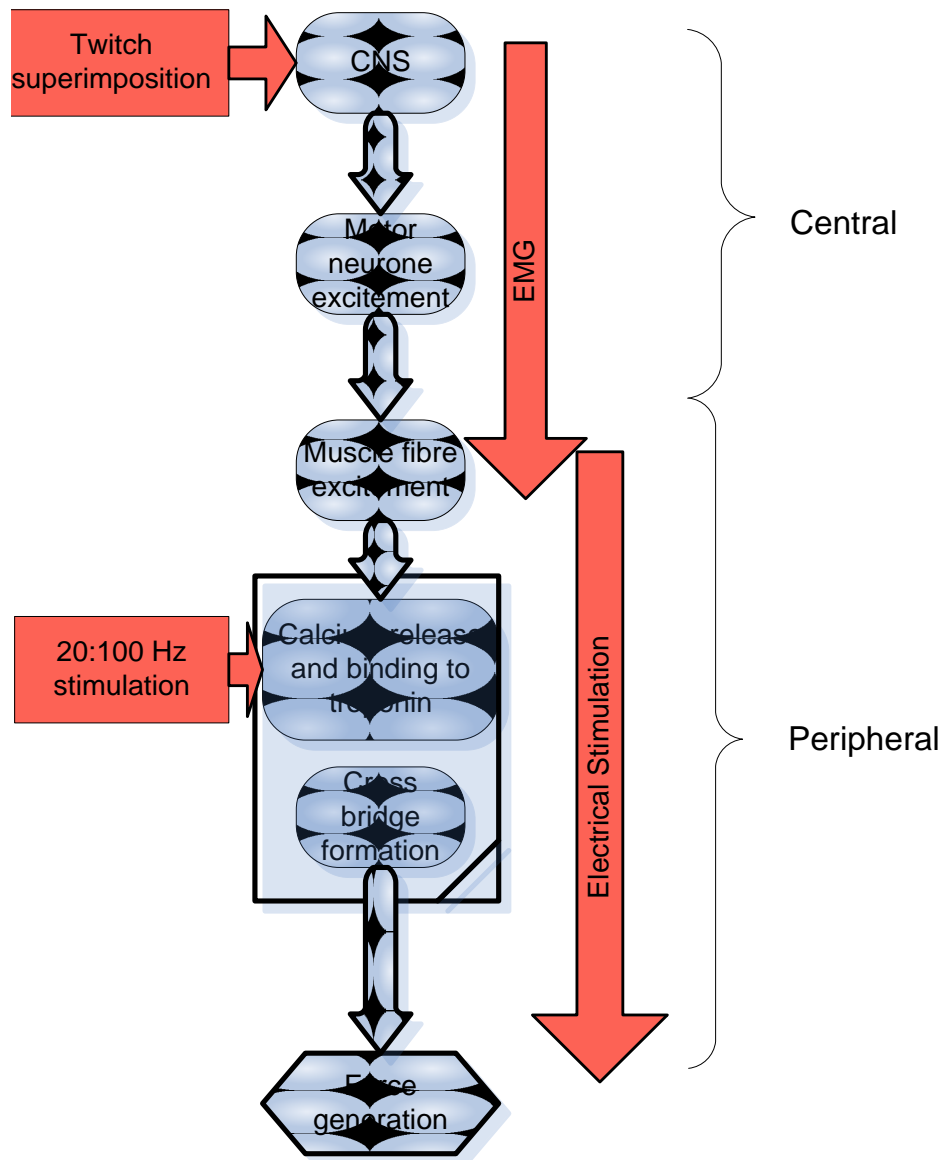
1. describe the physiological fatigue profile of the knee extensors in people with PN in comparison to healthy volunteers,
2. investigate the relationships between experienced fatigue and physiological fatigue in people with PN

This investigation, with that in Chapter Five, fulfils the second aim of this thesis by determining the fatigue profile of people with PN.

6.2.2. Possible causes of physiological fatigue

The source of physiological fatigue can lie within the central or peripheral nervous system, the muscle under test, or at all three sites. Central factors which produce physiological fatigue include the ability to fully activate muscles and changes that occur in peripheral nerves in response to activity. These are discussed on Page 194. Peripheral factors which cause a reduction in force output include alterations at the neuromuscular junction and within the muscle and are discussed on Page 195 (Bigland-Ritchie et al. 1983; Gandevia 2001). Central and peripheral factors, which are intricately related to each other, can be assessed separately to allow dissection of the cause of physiological fatigue. A simplified summary of techniques to measure central and peripheral factors of fatigue is presented in Figure 6-1 overleaf.

Figure 6-1 Potential sources of physiological fatigue and methods of their assessment.



CNS – central nervous system. Adapted from Vollestad et al. 1997.

6.2.3. Central factors of physiological fatigue

Central nervous system

Physiological fatigue mechanisms in the central nervous system (CNS) include decreased voluntary activation, or increased inhibition, and alterations in discharge frequency of spinal motor neurones (Gandevia 2001).

Voluntary activation

Voluntary activation is the ability to fully and voluntarily contract the muscle or muscles under test (Gandevia 2001). Decreased voluntary activation causes abnormal reductions in strength which appear as weakness (Gandevia 2001). Inhibition, or decreased activation, occurs after disuse (Duchateau and Hainaut 1998), injury (Dornonville de la Cour and Jakobsen 2005; Rutherford et al. 1986), if afferent proprioceptive information is impaired (Hurley et al. 1997) and is thought to be a protective, subconscious response to prevent injury or over work (Gandevia 2001; Rutherford et al. 1986). Some reports in people with neurological conditions show that voluntary activation is not significantly lower than healthy volunteers (Kent-Braun et al. 1994; White et al. 2004) whilst others demonstrate that it is significantly reduced (Gandevia et al. 2000). One small study has investigated the voluntary activation of the elbow flexors in ten people who complained of severe experienced fatigue after GBS (Garssen et al. 2005b). There were no significant differences in activation to healthy participants both at rest and after a two minute sustained contraction, indicating that voluntary activation was normal in people with PN, despite severe experienced fatigue (Garssen et al. 2005b). However, this study used a small number of participants (n=10) and only the elbow flexors were tested so the results cannot be generalised to other muscles or to the wider PN population. Abnormal physiological fatigue of a small or upper limb muscle is also less likely to markedly influence experienced fatigue as it may not affect daily performance. Voluntary activation of large, weight bearing muscle groups has not been assessed in people with inflammatory PN. If inhibition was present in muscles such as the knee extensors, it could elicit experienced fatigue as their inhibition will affect function. These deficits could contribute to more severe experienced fatigue but may be reduced by training (Rutherford and Jones 1986). Therefore, voluntary activation of the knee extensors requires assessment to see if deficits are present and to investigate any relationship with experienced fatigue in people with PN.

Peripheral nervous system

Changes in the peripheral nervous system can affect the drive to the muscle and thus force production. Activity dependent conduction block (ADCB) in peripheral nerves which have been demyelinated could produce physiological fatigue in people with PN, which may contribute to experienced fatigue (Cappelen-Smith et al. 2001; Kaji et al. 2000; Kaji 2003). In demyelinated nerves, the conduction of nerve impulses is slowed which results in a decreased driving current. If this driving current cannot overcome the threshold needed to cause depolarisation, conduction block occurs, resulting in temporarily and rapidly reduced muscle force (Kaji et al. 2000). Activity could elicit conduction block as a train of impulses, such as those required to

produce a sustained or repeated muscle contraction, can cause hyperpolarisation (Kaji et al. 2000). This increases the threshold for depolarisation which cannot be reached by the already reduced driving current in demyelinated nerves (Kaji et al. 2000). Activity dependent conduction block has been demonstrated in hand muscles after sustained voluntary contractions in people with MMN and CIDP, but its functional effects, if any, are not clear. If present, ADCB could result in loss of force during sustained activity, impairing function and potentially contributing to experienced fatigue. Although the presence of ADCB was not able to be investigated directly in this study, ADCB would be one cause of an abnormal force decline seen during fatiguing exercise and could then be specifically investigated in future work.

6.2.4. Peripheral factors of physiological fatigue

Neuromuscular junction

The neuromuscular junction appears largely normal after treatment in GBS and no disorders are reported beyond the acute period of GBS, in CIDP or PDN (Buchwald et al. 2002; Cappelen-Smith et al. 2001; Kaji et al. 2000; Kaji 2003; Kiernan et al. 2002; Kimura 2001). Therefore, changes at the neuromuscular junction are an unlikely source of physiological fatigue in this patient group. For this reason, the performance of the neuromuscular junction was not examined in this investigation.

Muscle factors

Delayed low frequency recovery

Alterations in sarcoplasmic calcium dynamics within muscles during exercise can produce long lasting force reductions which are most apparent on low frequency electrical stimulation (Jones 1996; Tupling 2004). This low frequency fatigue or delayed low frequency recovery (DLFR) can cause persistent physiological fatigue, lasting for several hours or even days (Westerblad and Allen 2002). It is caused by abnormalities in calcium ion regulation within the sarcoplasmic reticulum which affects muscle contraction, and is exacerbated by damage to sarcomeres by increased oxidative stress and high calcium transients during exercise (Tupling 2004; Westerblad and Allen 2002). Some report that increased DLFR contributes to physiological fatigue in people with multiple sclerosis (MS) (Lenman et al. 1989; Ng et al. 2004) and others hypothesise that DLFR could contribute to physiological fatigue in people with neuromuscular conditions, but this has not been investigated (Milner-Brown and Miller 1989). If present, increased DLFR would cause persistent physiological fatigue after exertion which, in turn, may worsen experienced fatigue in people with PN. Therefore, an investigation of DLFR is required to identify if abnormal levels are present in people with PN and to examine any association with the severity of experienced fatigue.

Muscle fatigability

Muscle fibre type determines the fatigability or fatigue profile of all muscles. The fatigue profile of a muscle may alter in response to changes in the relative proportions of muscle fibre types after alterations in motor unit size or after disuse or training, but this has not been directly

examined in people with inflammatory PN (Duchateau et al. 1998). Findings in conditions affecting the central nervous system are not likely to be applicable to PN as tonal changes are recognised to influence muscle fatigability (Lieber et al. 2004). However, Borg et al. (1988) examined muscle fibre type in 19 people after polio and found that the muscles which were most severely affected were markedly atrophied but retained a normal fibre type differentiation (Borg et al. 1988). However, in less severely affected muscles, there was a significant increase in the relative proportion of fatigue resistant fibres (Type I) (Borg et al. 1988). This was thought to be because people overused these muscles to allow continued function by compensating for those which were severely atrophied. Although the differences between PN and polio are acknowledged, these findings suggest that people with PN could have altered physiological fatigue in some muscles. This is supported by two studies which attributed greater muscular endurance of the ankle dorsiflexors and knee extensors in people after GBS to an increased proportion of fatigue resistant fibres (Andersen 1998; Dornonville de la Cour and Jakobsen 2005). Conversely, compensatory reinnervation which occurs in over 60% of patients with PN (Dornonville de la Cour et al. 2005), disuse during the acute illness and persistent reductions in activity would predict increased fatigability of muscle (Duchateau and Hainaut 1998). From this limited and equivocal evidence, people with PN may exhibit a combination of changes associated with disuse and increased motor unit size which would produce greater or lesser physiological fatigue. Therefore, in order to describe the physiological fatigue profile of people with PN, direct investigation of muscle fatigability is required.

6.3. Method

A cross sectional design was chosen to address the aims of this investigation (Sim and Wright 2000). Participants with a confirmed diagnosis of GBS, CIDP, MMN or PDN were recruited as described in Chapter Five.

Participants were asked to attend Shepherd's House, King's College London on two occasions, one week apart. Participants were instructed to avoid caffeinated beverages for 12 hours prior to testing (Spriet 1995) and not to eat a heavy meal or consume alcohol on the day of the test (American College of Sports Medicine 1995). Sample size was estimated from two studies as described in Chapter Five (Page 173).

6.3.1. Measurement of physiological fatigue

After completion of the questionnaires and physical tests described in Chapter Five, tests of physiological fatigue were performed in the knee extensor muscle group, which were tested on both visits. The limb to be tested, and the fatiguing protocol used (A or B) was randomly chosen on the first visit. The remaining protocol was performed on the same leg on the second visit.

The fatigue protocols used were designed to assess different aspects of physiological fatigue and are described in Section 6.3.4. Protocol A comprised repeated sub maximal contractions of the knee extensors in attempt to mimic daily activity and test aerobic muscle metabolism and function. Participants completed a sustained isometric maximal contraction in Protocol B to assess the response to predominantly anaerobic muscle work. This was followed by intermittent electrical stimulation to measure muscle fatigability.

One week was left between testing sessions to allow recovery but to minimise the chance of any changes in the participants' clinical status.

Testing position

Participants were comfortably seated on a Kin Com dynamometer (Chattanooga Corporation, USA) and firmly secured at the waist, hips and across the chest with adjustable straps (Figure 6-2). The hips were positioned in 80° flexion. The axis of the Kin Com was positioned by eye at the centre of rotation of the knee, which was flexed to 90°, and secured firmly above the malleoli to the lever arm via a cushioned cuff. Lever arm length (between the centre of the knee joint and ankle cuff) was not incorporated in force calculation, therefore linear forces were expressed in Newtons (N).

The Kin-Com dynamometer has previously demonstrated test re-test reliability in measurements of linear isometric knee extensor muscle force (Mayhew et al. 1994). Sixteen repeated measurements on the Kin-Com, with known forces of 49 to 196 Newtons, were reliable over three months (Coefficient of variation: 3%, calibration data shown in Appendix Five).

Two moistened, sponge covered electrodes were used to percutaneously electrically stimulate the knee extensors. They measured 12 cm x 7 cm, were placed proximally and distally on the anterolateral thigh and secured with bandages.

6.3.2. Measurement of surface electromyography

At each session surface electromyography (sEMG) was recorded from the rectus femoris, vastus medialis and vastus lateralis muscles in the tested leg. To ensure good electrode-skin contact, the skin was shaved if necessary, gently abraded and then cleaned with an alcoholic wipe (Basmajian and Deluca 1985). Once the skin was dry, two disposable, self adhesive EMG Ag/AgCl electrodes (recording area= 7.9 mm²) were placed on the muscles in the direction of the muscle fibres at an inter electrode distance of 20 mm (SENIAM 1999). The measurements of sEMG were not compared for the same participants between sessions, therefore the placement of electrodes was not marked on the skin. Placement positions are described in Table 6-1.

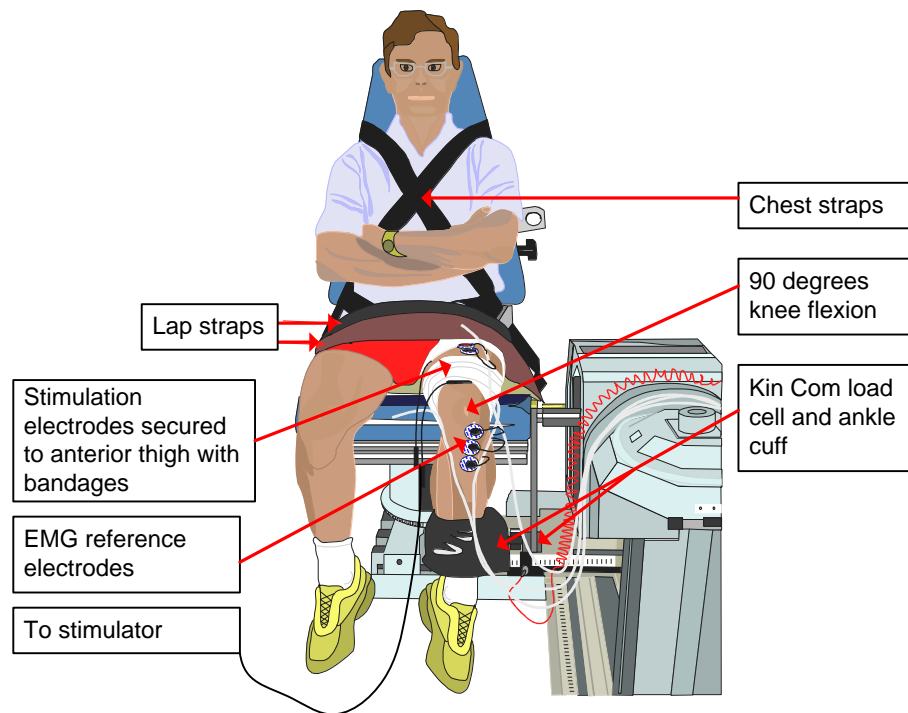
Table 6-1 Surface EMG electrode placements

Muscle group	Position
Rectus femoris	50% on the line from the anterior superior iliac spine to the superior patella.
Vastus medialis	80% on the line between the anterior iliac spine and the joint space of the medial ligament
Vastus lateralis	Two thirds on the line from the anterior superior iliac spine to the lateral patella
Reference electrodes	On the anterior tibia below the tibial tuberosity.

Adapted from the SENIAM guidelines (SENIAM 1999).

All sEMG data were recorded using the Biopac, MP 100 system (Biopac Systems Incorporated, USA). This system has a common mode rejection ratio of 100 dB at 50 to 60Hz. The gain was set at x1000 to produce a range of raw EMG amplitude from ± 1 Volt (Basmajian and Deluca 1985). High and low pass filters at 10 and 500 Hertz (Hz) were used.

Figure 6-2 Diagram to show position for testing of the knee extensors



Preliminary treatment of surface EMG

Surface EMG readings were recorded onto a personal computer via a 16 bit analogue to digital converter (1401, Cambridge electronic design, UK) at a frequency of 1200 Hz, and displayed using Signal software (version 2.13, Cambridge electronic design, UK). The DC offset was checked to be zero before each testing session. The root mean squared (RMS) sEMG amplitude was calculated over 250 milliseconds for RF, VM and VL muscles during MVC and 50% MVC contractions.

The RMS sEMG amplitudes during voluntary contractions for each muscle were normalised (nEMG) by dividing by the corresponding muscle RMS EMG from the baseline isometric MVC at each testing session.

The average RMS nEMG of knee extensors was also calculated, as the contribution of the RF, VM and VL muscle groups could change with physiological fatigue (Akima et al. 2002).

6.3.3. Testing procedure

After a short warm up, consisting of several sub maximal isometric knee extensions, participants were asked to perform five isometric MVCs of the knee extensors, each lasting three seconds, to familiarise themselves with the protocol. Force was recorded on a computer and simultaneously displayed on a monitor next to the participant using Signal software (version 2.13 Cambridge Electronic Design, UK).

Measurement of peak force

After a two minute rest participants performed several isometric MVCs, with 20 seconds rest between each contraction. Contractions were repeated until force did not increase further, and the peak force attained was noted.

Each participant was verbally encouraged throughout to “push as hard as you can” on each contraction (McNair et al. 1996). A monitor was also used to provide visual feedback throughout testing. The gain of the display was changed between sessions to maximise effort and activation (Gandevia 2001).

Measurement of voluntary activation

At both testing sessions, the ability to fully activate the knee extensors was assessed using the percutaneous twitch superimposition technique (Rutherford et al. 1986). This technique is considered reliable and sensitive if activation exceeds 40% (Herbert et al. 1997; Nørregard et al. 1997; Todd et al. 2004) and has been used widely in healthy subjects and a range of patient groups including people with post polio syndrome and MS (Horemans et al. 2004; Ng et al. 2004).

Three one Hertz (Hz), 50 microseconds (μ s), 400 Volt square wave impulses of 250 milliseconds duration were applied over three seconds using an electrical stimulator (Digitimer D4030, Digitimer Stimulator DS7, Digitimer, UK) via the moistened, sponge covered electrodes placed proximally and distally on the anterolateral thigh (Rutherford et al. 1986). The current was increased so that at least 10% of MVC force was produced by each impulse, and the twitch force reached a plateau (Nørregard et al. 1997).

Participants received three stimuli whilst at rest, and were then instructed to produce a MVC and “kick out as hard as possible”. Whilst participants maintained a MVC, the knee extensors were stimulated percutaneously so that three stimuli were coincident when force was maximum or near maximum. Participants were provided with visual feedback and verbal encouragement during each contraction to maximise activation (Gandevia 2001). Immediately on relaxation, three stimuli were applied to the relaxed muscle. This test was repeated three times.

The greatest force at which a twitch was applied during an MVC was identified. A resolution which allowed sensitivity to 0.5 N was used. If a superimposed twitch was visible, calculation of voluntary activation was performed using (Jakobi and Rice 2002):

$$\% \text{ activation} = 1 - \left(\frac{St}{Pt} \right) \times 100$$

St= superimposed twitch height. Pt= resting twitch height after MVC (potentiated twitch).

The potentiated twitch was consistently used as sufficient time was not available to allow rest between each measurement and it is likely that the superimposed twitch on near maximal contractions is potentiated (Folland and Williams 2007; Vandervoort et al. 1983).

Five participants' voluntary activation levels (three healthy and two PN participants) were recalculated on two occasions to establish the ability of the rater (the author) to reliably calculate voluntary activation. The mean difference between repeated calculations was less than 1% (0.78%, range 0-1.6%).

Measurement of low and high frequency stimulated muscle force

The presence of delayed low frequency recovery (DLFR, or low frequency fatigue) was investigated by measuring the force produced when the quadriceps was stimulated percutaneously at 20 Hz and 100 Hz (Jones 1996; Jones and Round 1990). A two second train of 100 Hz square wave (50 μ s, 400 Volts) was applied via the two electrodes, positioned as described previously. The stimulation current was increased to produce a force of 20 to 25% of MVC at 100 Hz stimulation and until plateau, if tolerated. This was to ensure a representative portion of the muscle was stimulated. A 20 Hz pulse was then applied at the same intensity for two seconds. The ratio of 20 Hz force to 100 Hz force was calculated at baseline and after fatigue Protocols A and B (Gibson et al. 1993; Jones 1996).

6.3.4. Fatiguing protocols

After completion of the baseline measurements described in Section 6.3.3, the knee extensors were fatigued in two different ways. The same leg was tested in both protocols.

Investigations of physiological fatigue have used a range of protocols to induce muscle fatigue. Some have used sustained muscle contractions (Garssen et al. 2005a; Lindeman et al. 1999; Milner-Brown et al. 1986), or intermittent contractions (Badier et al. 1993; Lanza et al. 2004; Lindstrom et al. 1997), a combination of both (Schwid et al. 1999; Seghers and Spaepen 2004), whilst others have chosen a ramped protocol which incrementally increases the force during intermittent contractions (Akataki et al. 2001). A ramped protocol was not utilised as it was anticipated that participants would require considerable familiarisation to achieve accurate incremental force production which in itself may elicit fatigue in some PN participants. Practically, it was also difficult to alter the scale of the monitor used to display the force trace quickly, meaning that participants would be unable to accurately obtain the required force. Therefore, intermittent contractions were chosen for Protocol A and a sustained contraction was used for Protocol B.

Protocol A

This protocol was designed to assess physiological fatigue during and after voluntary repeated muscle contractions in an attempt to mimic functional muscle work (Vollestad 1997) and was adapted from others used to induce physiological fatigue in people with post polio and chronic fatigue syndromes (Allen et al. 1994; Lloyd et al. 1988; Rodriguez and Agre 1991). Intermittent contractions also ensured that blood supply was not fully occluded and that muscles could be assumed to be working predominantly aerobically.

Participants performed repeated voluntary isometric knee extensions, at 50% of MVC force, while sEMG and force were measured continuously. Each contraction was maintained for six seconds, followed by four seconds rest. Ten repetitions were performed consecutively and

formed one set. After the tenth contraction, participants were asked to rate their perceived exertion using the 6-20 Borg scale (Borg 1970) (as described in Chapter Five).

Participants were provided with continuous visual feedback to allow accurate development of force. A metronome was used to indicate the duration of each contraction and rest period. After sets one, three, five and seven participants performed an MVC. Standardised verbal encouragement was given throughout.

The protocol continued until participants were unable to produce forces above 40% MVC on two contractions, wished to stop, or had completed eight sets (80 repetitions).

Recovery

Recovery was monitored for ten minutes on completion of the protocol, by measuring the sEMG during 50% MVC contractions and perceived exertion at 10 seconds, 30 seconds, one minute, 90 seconds, two, four and ten minutes. A final MVC and 20 Hz and 100 Hz stimulation were also performed at ten minutes.

Protocol B

Protocol B was designed to measure the physiological fatigue elicited by predominantly anaerobic muscle work as participants performed an isometric MVC for one minute. After ten minutes recovery, intermittent electrical stimulation was also used to directly estimate the fatigability of the knee extensors muscle group.

Sustained isometric contraction

After baseline measurements, participants performed an isometric MVC of the knee extensors for one minute, while force and sEMG were measured. All participants were instructed to breathe regularly during the sustained contraction, and to relax the upper limbs to avoid large changes in blood pressure (O'Connor et al. 1989). Verbal encouragement was given throughout. A fatigue index for the change in force (FI) was calculated from (Milner-Brown and Miller 1989):

$$\text{Fatigue Index (\%)} = \left[\frac{\text{Final Force (60 seconds)}}{\text{Initial Force (1 second)}} \right] \times 100$$

The test re-test reliability of the fatigue index was investigated in one healthy and one PN participant from two repeated measurements, one week apart. The fatigue index varied by 3% in both participants (coefficient of variance: 6%).

Power spectra of EMG during the sustained MVC

The power spectra of the EMG of the RF, VM and VL muscles at the start and end of the 60 second isometric MVC were obtained by applying a Fast Fourier Transform (size: 256) to raw EMG signals (James 1995). The median value of frequencies between 10 and 300 Hz were then calculated. The median power frequency was calculated for each muscle during the first and final second of the 60 second isometric MVC. The median power frequency was used in

preference to the mean as it is less affected by signal noise (Basmajian and DeLuca 1985; Jurrell 1998).

Recovery

A MVC was performed after 90 seconds of recovery and the force produced by low and high frequency stimulation was measured at ten minutes.

Electrically induced fatigue

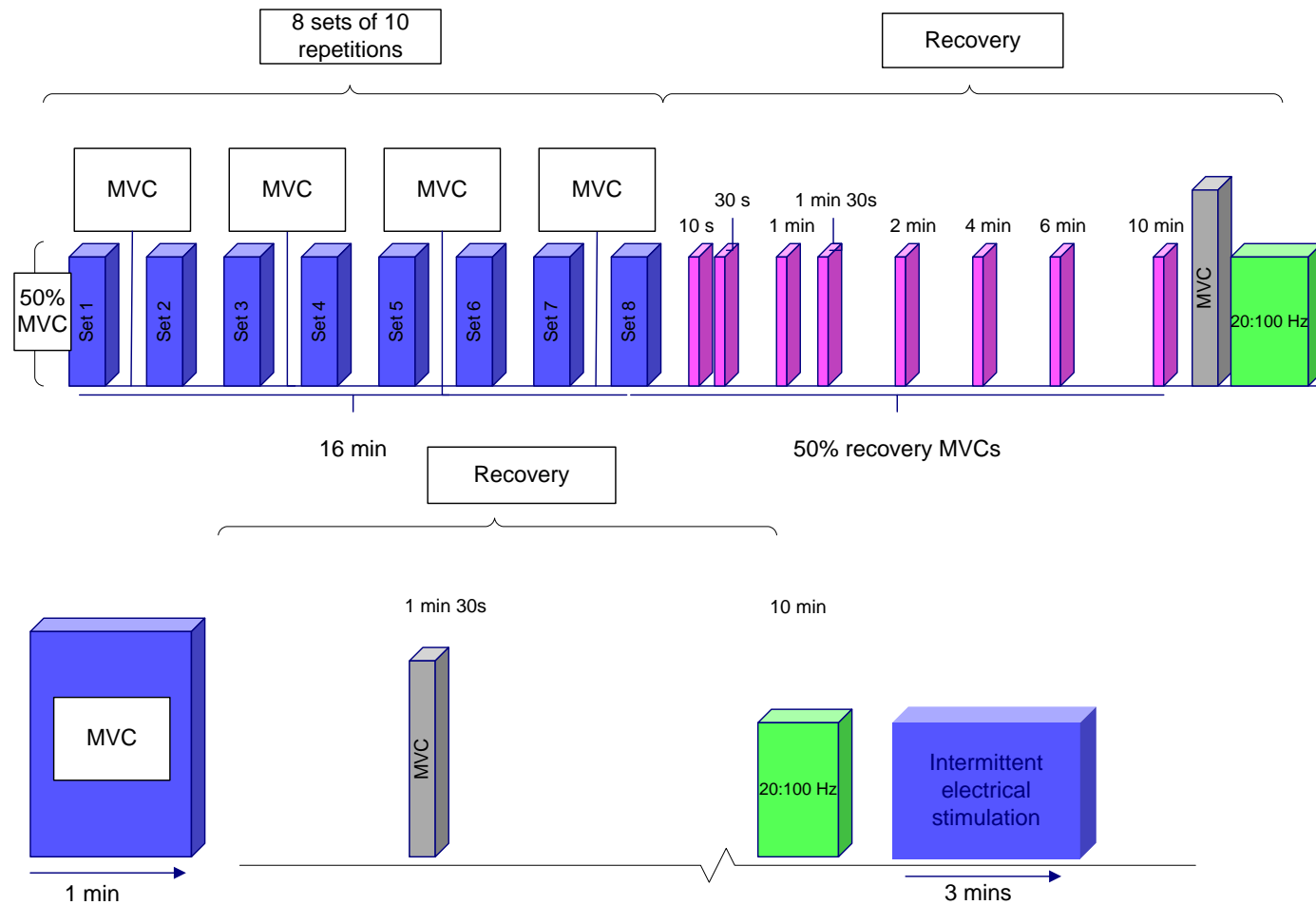
After ten minutes rest, percutaneous electrical stimulation at 40 Hz (50 μ s, 400 Volt square wave impulses) was applied for 250 ms every second for three minutes (180 impulses) via the two electrodes positioned as described previously (Burke et al. 1973; Lenman et al. 1989). The current was adjusted so that the stimulated force was approximately 25% of MVC. This technique has been used previously to indicate muscular fatigue in healthy participants and several patient groups including people with MS and spinal cord injury (Lenman et al. 1989), but not in people with PN.

Participants were instructed to relax throughout the test and to avoid tensing the leg. The decline in force from the first stimulation indicates the profile of muscle fibre fatigability and muscle metabolism. It was calculated by expressing the force produced by the 180th impulse as a percentage of the force produced by the first.

Measurements taken one week apart were moderately reliable in one healthy participant (coefficient of variance of 4%). The effect of the sustained MVC and recovery contractions upon the decline in force during electrically induced fatigue was investigated in one PN participant, who repeated the electrically induced fatigue test on a third occasion. There was a +6% difference in the decline in force during the electrically induced fatigue test after completing the sustained MVC compared to the when the test was repeated in the rested muscle.

A schematic diagram of fatiguing protocols A and B is shown in Figure 6-3.

Figure 6-3 Diagram to show fatigue Protocols A (top) and B (bottom)



6.3.5. Analysis

Peak MVC force was normalised by dividing by body weight, to account for gender differences between groups (Pincivero et al. 2004).

The ratio between force and RMS nEMG of the knee extensors was calculated for baseline MVCs and during the 60 second sustained MVC during Protocol B. This Torque:EMG ratio (TER), or neuromuscular efficiency, has been shown to demonstrate differences between healthy and PN participants more clearly than EMG or force readings alone in previous studies of PN (Lindeman et al. 1999). It is calculated from (Lindeman et al. 1999):

$$\text{Torque : EMG ratio (N mV}^{-1}\text{)} = \frac{\text{MVC force (Newtons)}}{\text{Mean RMS nEMG (RF, VM, VL) milliVolts}}$$

Two tailed independent t tests assuming unequal variance were used to assess differences between healthy and PN participants in MVC force in the knee extensors, voluntary activation, RMS nEMG, TER, 20:100 Hz stimulation at baseline and after fatigue protocols, and the fatigue index and decline in force after intermittent electrical stimulation.

The MVC force, RMS nEMG, TER and 20:100Hz stimulation after the fatigue protocol were compared to pre-fatigue values using two tailed paired t tests for each group.

Differences in force and RMS nEMG amplitude parameters between healthy and PN groups during the fatigue protocols and recovery were examined using repeated measures analysis of variance (ANOVA).

Differences between PN participants who reported severe experienced fatigue (PNF) and those who did not (PNN) were examined using descriptive statistics and Mann Whitney tests, as small numbers meant the data were not normally distributed.

Associations between strength, activation and age were assessed for both groups using Pearson's correlation coefficients. The association between strength, activation and fatigue index with experienced fatigue severity, activity limitations, participation, EO_2 , and resting heart rate (from Chapter Five) was also assessed using Spearman's and Pearson correlation coefficients. The size of correlation coefficients were judged to be low/weak (0.1-0.3), moderate (0.3-0.6) or large/strong (>0.6) according to published criteria (Cohen 1977).

No adjustments were made for multiple comparisons (Perenger 1998). Significance was set all $p < 0.05$ for all tests. All data were analysed using SPSS© software (SPSS Inc. version 11.5.1).

6.4. Results

6.4.1. Participants

Fifteen people with PN volunteered, but one could not tolerate electrical stimulation and one other could not attend both testing sessions. Therefore 13 participants (four females) with PN were recruited and completed all measurements. Thirteen healthy volunteers (seven females) were also recruited from staff and students of King's College London. Participant characteristics are shown in Chapter Five in Table 5-3 on Page 175. There were no significant differences between healthy participants and those with PN for demographic characteristics of age, weight, height and BMI.

Local ethical approval was obtained from Guy's and King's College London research ethics committees and all participants gave written informed consent.

Eight PN participants (one female) reported levels of severe experienced fatigue that persisted for more than six months (PNF), the remainder ($n=5$, three females) did not report severe fatigue (PNN).

6.4.2. Baseline measurements

Knee extensor force

Knee extensor force is shown in Table 6-2. When peak linear MVC force was normalised to weight, healthy people were significantly stronger than PN participants. There were no significant differences in peak MVC knee extensor force between session one and two for PN or healthy groups. Interestingly, PNF participants were slightly stronger than those with no fatigue (PNN) but this was not statistically significant (Table 6-2). Age was not significantly or strongly associated with peak extensor force for either group (both $r < 0.4$).

Surface EMG

Repeated RMS sEMG measurements during MVC did not differ significantly between session one and session two, therefore mean values were used in all comparisons. When the sEMG was expressed relative to peak force produced during the initial MVC (Torque:EMG ratio, TER, Lindeman et al. 1999), there were no significant differences between healthy and PN participants, nor between PNF and PNN participants. This is shown in Table 6-2.

Voluntary Activation

There was no difference in levels of voluntary activation between measurements taken one week apart. The mean voluntary activation of PN participants was not significantly different to healthy people, but was somewhat higher. There were no significant differences between PNN and PNF participants (Table 6-2).

Age, gender and peak force were not significantly or strongly associated with voluntary activation in either group (PN: all $r < 0.3$; Healthy: all $r < 0.5$).

Table 6-2 Strength, voluntary activation, Torque:EMG ratio and 20:100 Hz force ratio in the knee extensors of PN and healthy participants

	Healthy (n=13)	PN (n=13)	p H vs PN	PNF (n=8)	PNN (n=5)	p PNF vs PNN
Normalised strength (N Kg ⁻¹)	7.5 ±2.2	5.4 ±2*	0.002	6.2 ±8	4.1 ±1.9	ns
Strength (N)	476.4 ±122	433 ±161	ns	476 ±123	364 ±215	ns
TER (N mV ⁻¹)	1.58 ±0.4	1.4 ±0.4	ns	1.5 ±0.4	1.76 ±0.9	ns
Voluntary activation (%)	85 ±10	92 ±7	ns	90.4 ±9	94 ±7	ns
20:100 Hz stimulation ratio	0.67 ±0.1	0.58 ±0.13	ns	0.6 ±0.3	0.55 ±0.2	ns

All values are the mean ±SD of baseline values on two occasions. TER: Torque: EMG ratio.* denotes significant difference at p<0.05

Low and high frequency stimulation

There were no significant differences between baseline measurements of 20:100 Hz stimulated force taken one week apart in either group, suggesting that participants had recovered fully between each testing session. There were also no significant differences between PN and healthy or PNN and PNF participants (Table 6-2).

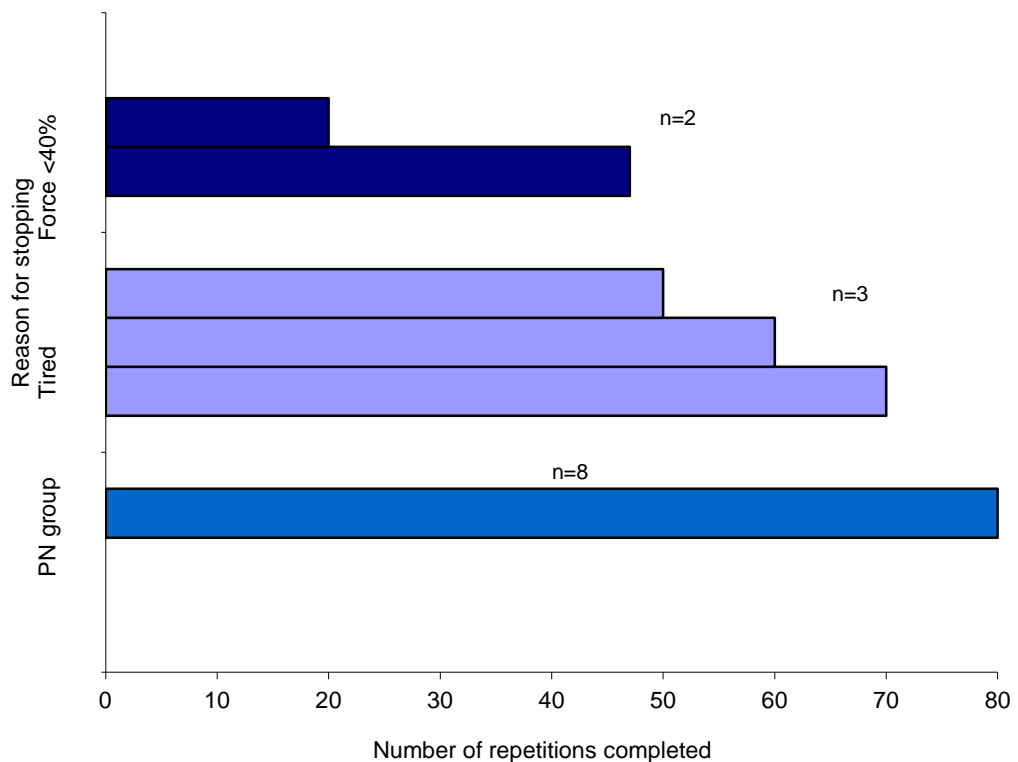
6.4.3. Protocol A

In Protocol A, participants performed up to 80 repetitions at 50% MVC force. All healthy volunteers completed all repetitions, as did eight PN participants. However, five PNF participants were unable to complete 80 repetitions. The number of repetitions completed in the PN group and the reason for stopping are shown in Figure 6-4.

Two PN participants were stopped as they were unable to continue generating forces above 40% of MVC, a criterion for stopping the test. One stopped after 20 repetitions and one after 47. Three PN participants stopped as they felt too tired to continue, despite maintaining force, after 50, 60 and 70 repetitions.

There were no significant differences in the mean voluntary activation and peak MVC force between PN participants that did complete the protocol (mean ±SD: 95.2% ±4; 4.7 N Kg⁻¹ ±1.8) and those that did not (87% ±7.7; 6.3 N Kg⁻¹ ±2).

Figure 6-4 Number of repetitions completed during Protocol A and reasons for non-completion.



Changes in surface EMG

During repeated contractions at 50% MVC, a significant increase in RMS nEMG for RF, VM, VL and the mean nEMG was seen in healthy and PN groups. These changes were not significantly different between PN and healthy groups during Protocol A. Changes in RMS nEMG from initial MVC values during Protocol A and recovery are shown in Figure 6-5 and Figure 6-6 overleaf.

The change in RMS nEMG from the first to the last completed 50% MVC during Protocol A was also examined to include PN participants that did not complete the entire protocol. These changes were not significantly different between healthy and PN groups. There was also no significant difference between PN participants who completed all contractions and those who did not, or between PNF and PNN participants.

Figure 6-5 RMS nEMG during Protocol A and recovery for healthy participants

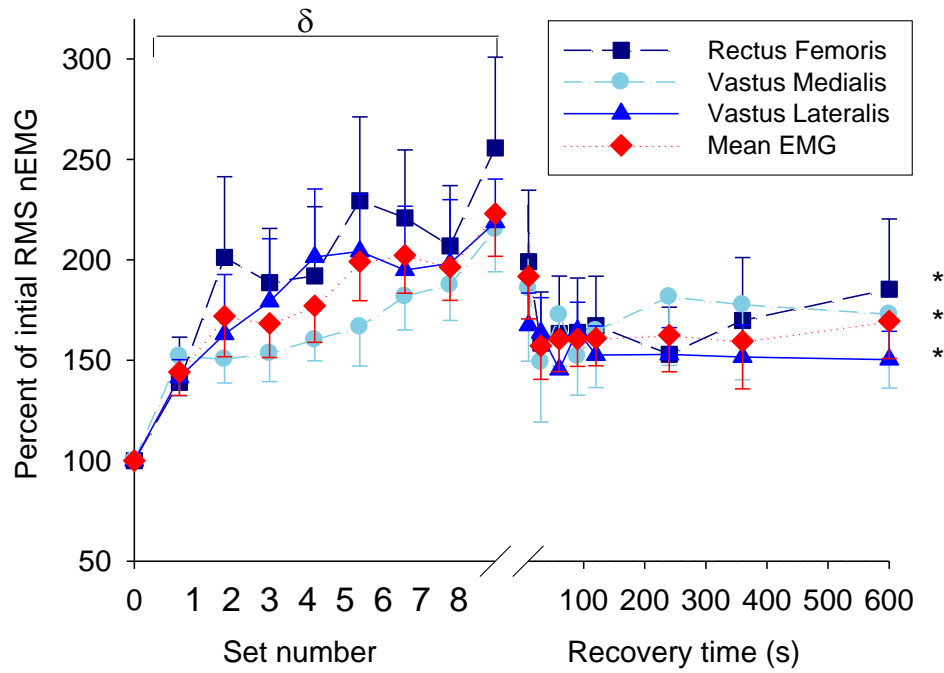
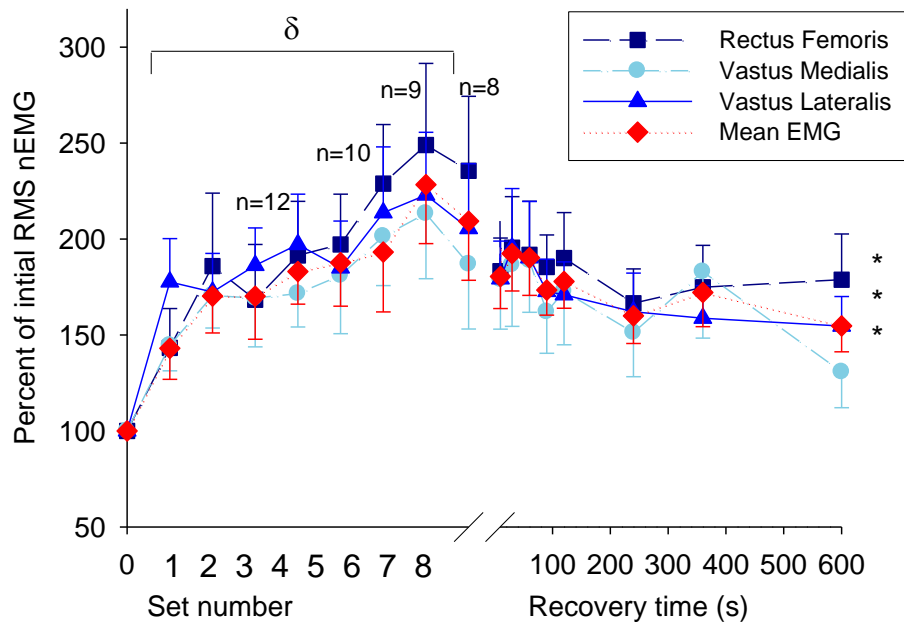


Figure 6-6 RMS nEMG during Protocol A and recovery for PN participants



δ denotes a significant increase in RMS nEMG for RF, VM, VL and mean EMG from 1st to 80th contraction. * indicates a significant difference between EMG activity at 10 minutes recovery and the 1st contraction (100%) for the RF, VL and mean EMG. The number of PN participants remaining during the protocol are shown. There were no significant differences between PN and healthy groups. Error bars denote one standard error of the mean.

Changes in RMS nEMG during 50% MVCs during recovery

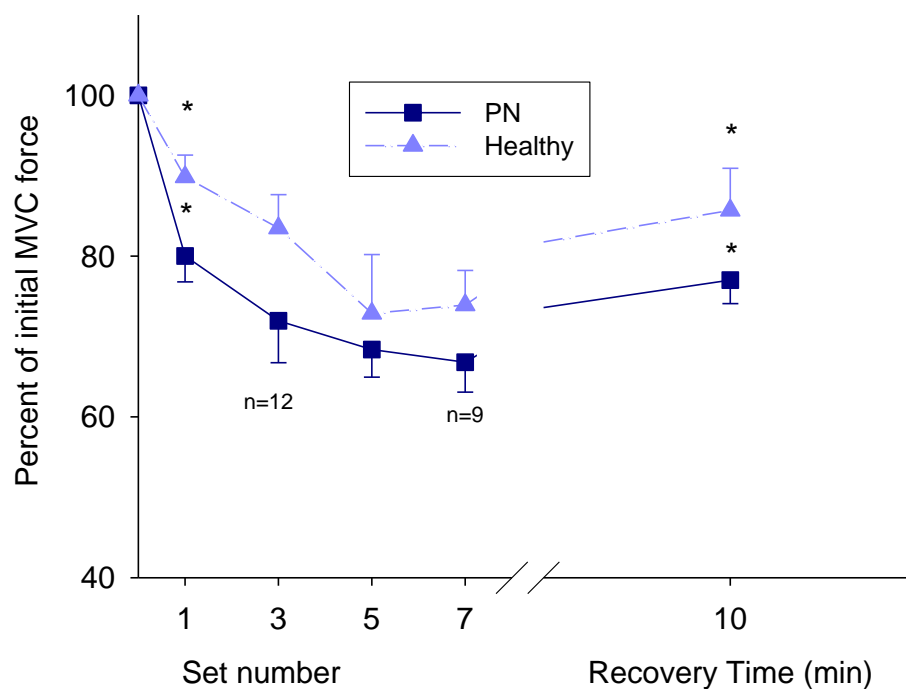
During the recovery period, there were no significant differences in RMS nEMG for any muscles between healthy and PN participants, nor between PNF and PNN participants (Figure 6-5 and Figure 6-6).

After ten minutes of recovery, the RMS nEMG of the VM muscle was not significantly different to that during the first 50% MVC of the first set for both healthy and PN groups. However, RF, VL and mean RMS nEMG remained significantly elevated for both healthy and PN participants.

Changes in MVC force during fatigue and recovery

There was a significant decrease in MVC force in both groups from baseline after the first set of fatiguing contractions. This was slightly larger in the PN group but not significantly different to healthy participants. The percentage of change in MVC force is shown for both groups in Figure 6-7.

Figure 6-7 Decrease in MVC force for healthy and PN participants during Protocol A



* denotes significant difference from baseline MVC force. Error bars denote one standard error of the mean. There was no significant difference between healthy and PN groups.

Peak MVC force remained significantly decreased from baseline MVC after ten minutes of recovery in both groups (Table 6-3). There were no significant differences in changes in MVC force between PN participants who completed all fatiguing contractions and those who did not, nor between PNN and PNF participants (Table 6-3).

Changes in RMS nEMG activity during fatigue and recovery

Both groups demonstrated significant increases in RMS nEMG from the baseline MVC to the MVC performed after one set of fatiguing repetitions in RF, VM and VL muscle groups ($p < 0.001$). This is shown in Figure 6-8 for healthy participants and in Figure 6-9 for PN participants. There were no significant differences between healthy and PN groups for any muscle during MVCs. Similarly, the RMS nEMG for all muscles in both groups remained significantly higher than baseline MVC values after ten minutes of recovery.

There were also no significant differences in RMS nEMG on the last completed MVC during Protocol A between PN participants that completed all repetitions and those who did not.

Change in 20:100 Hz stimulated force ratio

The ratio of force produced by 20 and 100 Hz electrical stimulation was assessed at baseline and after ten minutes of recovery from Protocol A and is shown in Table 6.3.

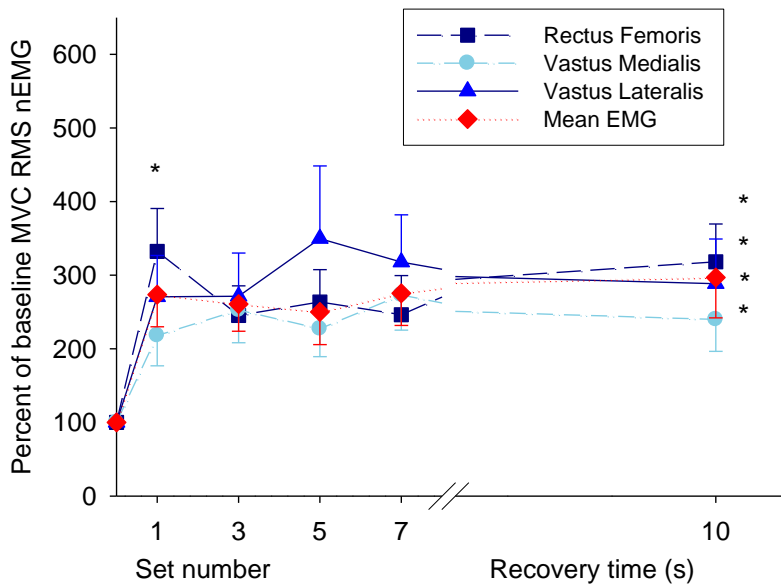
The ratio was significantly reduced from baseline in healthy and PN participants ($p < 0.001$). Despite the decrease in the PN group being somewhat larger, there was no significant difference between groups. There were also no significant differences in the decrease in the 20:100 Hz ratio between PNF and PNN participants. Similarly, the decrease in PN participants who did not complete all repetitions in Protocol A was slightly larger than other PN participants, but was not statistically different.

Table 6-3 Change in MVC force and 20:100 Hz ratio in Protocol A

	Change (Newtons) from baseline MVC to MVC at:				Change in 20:100 Hz force	p
	10 reps	70 reps	Recovery	p		
Healthy	38 ±56*	133 ±102	63 ±109*	ns	0.08 ±0.09*	ns
PN	80 ±46*	136 ±57	83 ±42*		0.14 ±0.1*	
PNF	98 ±49	164 ±24	92 ±45	ns	0.16 ±0.11	ns
PNN	55±29	114 ±69	69 ±38		0.12 ±0.09	
PN non C	98 ±63	-	89 ±44	ns	0.19 ±0.13	ns
PN C	69 ±31	-	80 ±43		0.12 ±0.07	

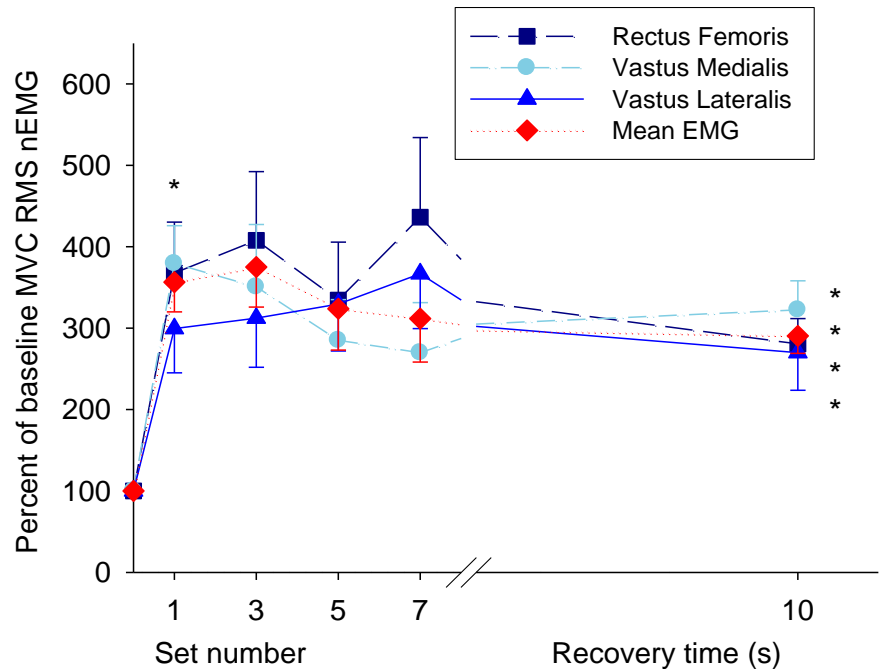
* denotes within group significant difference from baseline at $p < 0.05$ (not tested after 70 repetitions). All changes were negative, indicating a decline in force. PN non C- PN participants who did not complete 80 repetitions (n=5), PN C - PN participants who completed 80 repetitions (n=8).

Figure 6-8 Healthy RMS nEMG for MVC during fatigue Protocol A and after 10 minutes of recovery.



* denotes significant difference from baseline MVC.

Figure 6-9 RMS nEMG for MVC for PN participants during fatigue Protocol A and after 10 minutes of recovery



* denotes significant difference from baseline MVC.

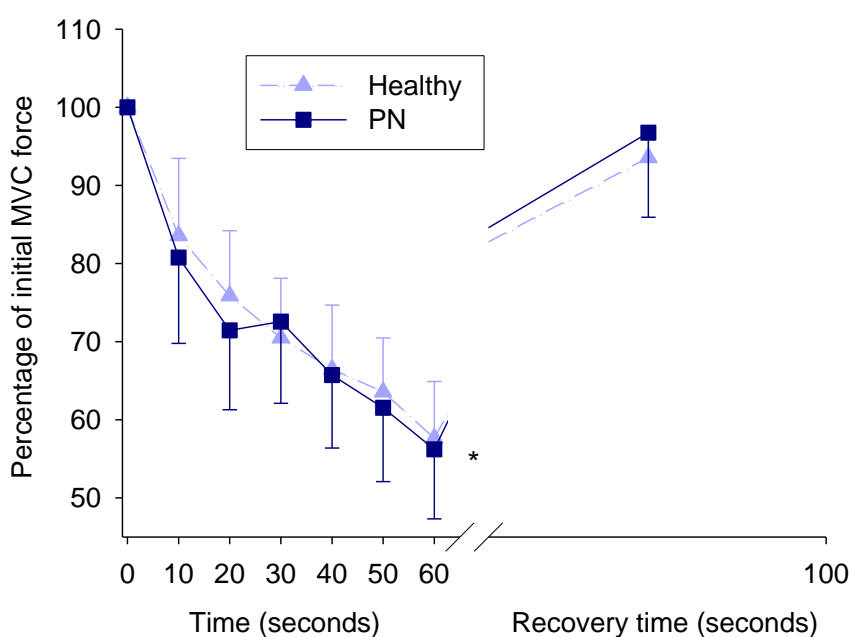
6.4.4. Protocol B

Changes in force and sEMG in response to a sustained isometric MVC

Changes in force and sEMG during and after a 60 second sustained MVC are shown in Table 6-4.

At the end of the isometric sustained 60 second MVC, the fatigue index of healthy and PN participants were similar (Table 6-4 and Figure 6-10). The fatigue index was also not significantly different between PNF and PNN participants.

Figure 6-10 Change in force during a 60 second sustained MVC and MVC at 90 seconds after completion.



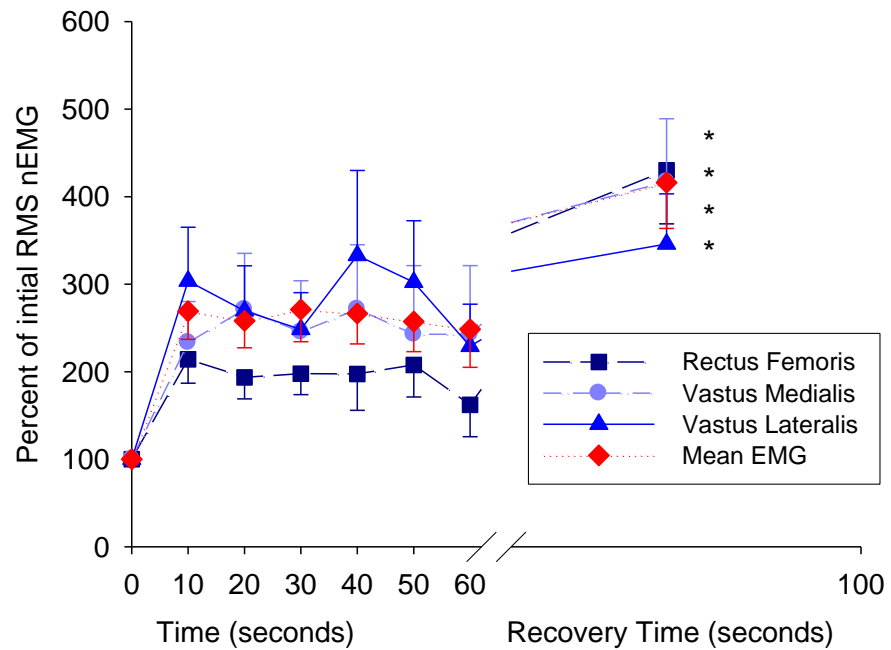
* denotes significant difference between initial MVC and force at 60 seconds at $p < 0.05$ for both groups. Error bars denote one standard error of the mean.

Correlations between initial MVC force and the fatigue index were neither strong nor significant for PN or healthy participants ($r < 0.5$).

Force in both healthy and PN participants recovered quickly as a MVC performed at 90 seconds after completion of the sustained contraction was not significantly different to baseline values (Figure 6-10), although RMS nEMG remained significantly higher for both as shown in Figure 6-11 for healthy volunteers and Figure 6-12 for PN participants.

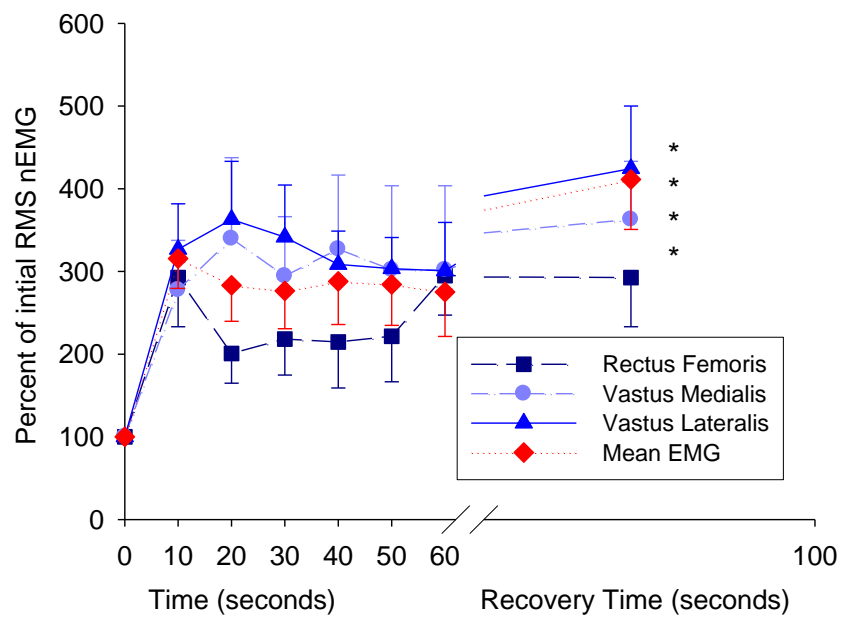
Both groups demonstrated similar changes in the RMS nEMG amplitude during and after the 60 seconds MVC (Figure 6-11 and Figure 6-12) and there were no significant differences between groups. There were also no significant differences between PNF and PNN participants.

Figure 6-11 Change in RMS nEMG for healthy participants during 60 second isometric contraction and recovery MVC at 90 seconds.



* denotes significant difference at 90 seconds recovery from baseline MVC at $p < 0.01$. Error bars denote one standard error of the mean.

Figure 6-12 Change in RMS nEMG for PN participants during 60 second isometric contraction and recovery MVC at 90 seconds.



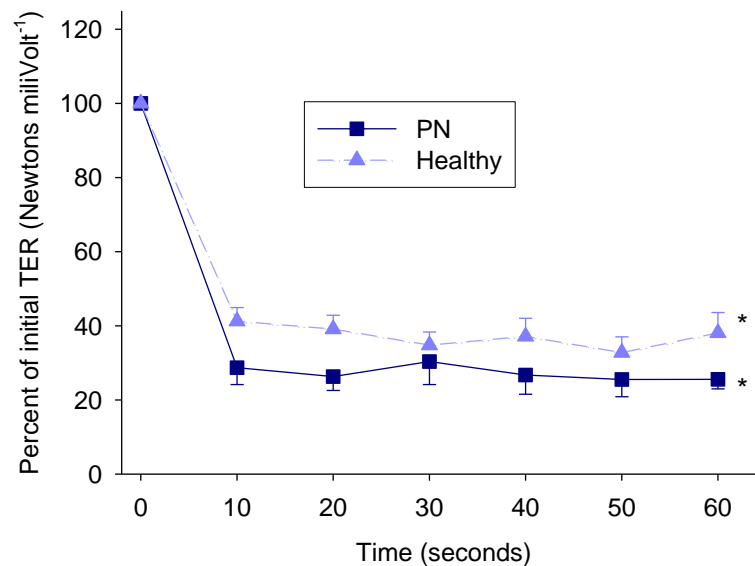
* denotes significant difference at 90 seconds recovery from baseline MVC at $p < 0.01$. Error bars denote one standard error of the mean.

Changes in the torque:EMG ratio during a 60 second sustained MVC

The TER was calculated for healthy and PN participants throughout the 60 second MVC and is shown in Figure 6-13. The TER values at 60 seconds were significantly lower than baseline for both groups ($p < 0.01$, Table 6-4).

There were no significant differences between healthy and PN groups, implying both groups had similar neuromuscular efficiency. Similarly, the change in TER was not significantly different between PNN and PNF participants.

Figure 6-13 TER for healthy and PN groups during 60 second MVC.



* denotes significant difference from baseline for both groups ($p < 0.01$). Error bars denote one standard error of the mean.

Changes in EMG median frequency after fatigue

The median frequencies at the start and end of the sustained MVC are shown in Table 6-5. Healthy participants demonstrated a significant decrease in the median frequency of the RF and VM muscles after the sustained MVC. The change in frequency in the PN group was somewhat smaller and was not significant in any muscles after the sustained MVC. However, the change in median frequency was not significantly different between groups, nor between PNF and PNN participants.

Changes in the ratio of low and high frequency stimulated force after a 60 second MVC

Changes in the 20:100 Hz stimulated force are shown in Table 6-4. The ratio of 20:100 Hz stimulated force was significantly decreased from baseline in both groups, after completion of a 60 second sustained isometric contraction and ten minutes recovery. This change was not significantly different between healthy and PN groups. There was a slightly greater decline in

the ratio in PNF participants when compared to PNN, inferring increased DLFR, but this was not statistically significant.

Changes in force produced by intermittent electrical stimulation

The force decline after three minutes of percutaneous intermittent stimulation is shown Table 6-4. There was no significant difference between healthy and PN groups, nor between PNN and PNF participants.

Table 6-4 Changes during Protocol B

	Fatigue Index (%)	Change in TER (Newtons)	Change in 20:100 Hz force	Force decline after electrical stimulation (%)
Healthy	59 ±18	485 ±233*	0.11 ±0.15*	63 ±11
PN	60 ±14	374 ±134*	0.13 ±0.18*	60 ±13
PNN	60 ±7	297 ±82	0.06 ±0.05	62 ±7
PNF	60 ±17	421 ±143	0.17 ±0.22	59 ±16

* denotes significant decline from baseline at $p < 0.05$ in both groups. There were no significant differences between groups. Values are mean ± SD.

Table 6-5 Changes in power spectra after a sustained MVC

Initial and final median frequency, Hz (range)										
	Healthy		PN		p	PNN		PNF		p
	Initial	Final	Initial	Final		Initial	Final	Initial	Final	
Rectus Femoris	67 (51-86)	53 (33-81) ^δ	61 (34-85)	53 (35-74)	ns	56 (34-67)	42 (35-55)	65 (47-85)	59 (48-74)	ns
Vastus Medialis	60 (47-99)	44 (27-62) ^δ	60 (43-97)	50 (31-78)	ns	55 (43-66)	44 (33-66)	63 (43-98)	53 (31-77)	ns
Vastus Lateralis	58 (39-84)	51 (28-84)	49 (31-78)	46 (35-60)	ns	50 (27-61)	43 (35-47)	49 (31-66)	47 (35-60)	ns

^δ denotes a significant decrease in median frequency from 1 to 60 seconds at $p < 0.05$ in the healthy group. There were no significant differences between groups.

6.4.5. Associations between experienced fatigue, activity, fitness and physiological fatigue

In PN participants, experienced fatigue measured on the FSS, FIS and PFS (from Chapter Five) was not associated with knee extensor strength, TER, voluntary activation, decrease in 20:100 Hz stimulated force after a 60 second MVC or the percentage decrease in electrically stimulated force after three minutes of intermittent stimulation (Table 6-6). Physiological fatigue measures were also not significantly associated with scores on the ONLS, SF-36 and Rotterdam Handicap questionnaires as shown in Table 6-6.

In healthy participants, the fatigue index during an isometric sustained MVC was significantly associated with increased fatigue measured on the PFS questionnaire ($r=0.6$) but no other significant associations were seen.

Table 6-6 Associations between experienced and physiological fatigue, activity, activity limitations, participation, energy and resting heart rate for PN participants

	FSS	FIS	PFS	ONLS	RHS	SF-36 PCS	SF-36 MCS
Strength (N kg ⁻¹)	0.47	0.38	0.31	-0.16	0.44	0.08	-0.5
Voluntary activation	-0.4	-0.24	-0.24	-0.44	-0.04	0.31	0.26
DLFR	0.12	-0.13	0.19	-0.26	0.27	0.13	-0.01
Fatigue index (%)	-0.1	-0.5	-0.4	-0.39	-0.15	-0.02	0.47
TER	0.1	-0.1	-0.36	-0.04	-0.3	-0.16	0.24
Force decline after electrical stimulation (%)	0.01	0.06	-0.04	0.28	-0.4	-0.23	0.09

All associations were not statistically significant at $p<0.05$. SF-36 PCS and MCS – SF-36 physical and mental component summary scores, DLFR – delayed low frequency recovery expressed as decrease in 20:100 Hz stimulated force after 60 second sustained MVC (Protocol B), TER – torque:EMG ratio on baseline MVC.

6.4.6. Summary of physiological fatigue results

Table 6-7 Main findings of physiological fatigue tests

Measure	Healthy vs PN	PNN (n=5) vs PNF (n=8)
Strength (N Kg ⁻¹)	Healthy significantly stronger than PN	No significant difference but PNF slightly stronger
Activation (%)	No significant difference but PN group had slightly higher activation	No significant difference
20: 100 Hz stimulation ratio	No significant difference	No significant difference
TER (N mV-1)	No significant difference	No significant difference
Protocol A:	All healthy completed; 5 from 13 PN (38%) did not complete	All PNN completed; 5 from 8 PNF (62%) did not complete
RMS nEMG during 50% MVC	No significant difference	No significant difference
MVC force during Protocol A and recovery	No significant difference	No significant difference
RMS nEMG during MVC	No significant difference	No significant difference
Decrease in 20:100 Hz ratio after Protocol A	No significant difference	No significant difference
Protocol B :		
Force during sustained MVC	No significant difference	No significant difference
RMS nEMG during sustained MVC and recovery	No significant difference	No significant difference
TER	No significant difference	No significant difference
Median Frequency	No significant difference but healthy group had significant decrease in RF and VM muscles	No significant difference
Decrease in 20:100 Hz ratio after sustained MVC	No significant difference	No significant difference but somewhat greater decrease in PNF participants
Force change after intermittent electrical stimulation	No significant difference	No significant difference

6.5. Discussion

This study described the physiological fatigue profile of the knee extensor muscles of people with inflammatory PN and compared findings with those from healthy volunteers. These aspects of fatigue have not been investigated previously in this patient group and, with the findings of Chapter Five, provide important indications of the potential contributors to experienced fatigue in PN.

The knee extensors were selected for investigation as they are vital to the performance of many functional activities in ambulant individuals and so their fatigue is likely to impact greatly upon activities and participation. It is acknowledged that the fatigue profile of each of the four muscles within the quadriceps and other knee extensors may differ to each other and other muscles as fibre type composition varies (Milner-Brown et al. 1986). Other muscles that may limit ambulant mobility such as tibialis anterior, are often affected in people with PN but practical factors (such as equipment provision) meant that this muscle could not be tested in this study. Muscles used in respiration are also likely to impact upon exercise endurance and aerobic capacity in people with PN, and so could contribute to experienced fatigue, but again could not be measured for practical reasons.

The knee extensors of PN participants were significantly weaker than those of healthy participants (H: $7.5 \pm 2.2 \text{ N Kg}^{-1}$; PN: $5.4 \pm 2 \text{ N Kg}^{-1}$), showing that they were affected by neuropathy or deconditioning due to disuse, but peak force was not significantly associated with experienced or physiological fatigue in either group. These findings agree with others who reported no significant associations between experienced fatigue measured on the FSS and MRC sum scores in 113 people with PN (Merkies et al. 1999).

As shown in Table 6-2, participants with PN had similar levels of voluntary activation to healthy people (mean \pm SD H: $85 \pm 10 \%$; PN: $92 \pm 7\%$). These results are also supported by Garssen et al. (2005b) who found no difference in voluntary activation of the biceps brachii muscle in ten people with severe experienced fatigue after GBS when compared to healthy volunteers. Full activation (100%) of the knee extensors was not expected in this study as evidence indicates that with greater sensitivity in testing, adults may only be able to activate the quadriceps femoris muscle to between 85-95% despite maximal effort (Folland and Williams 2007; Shield and Zhou 2004). This suggests that, despite people with PN being significantly weaker than healthy participants in this study, this was not attributable to an inability to fully activate the muscle.

Due to the design of the study, voluntary activation was not assessed in either group after the fatigue protocols, as the onset of delayed low frequency recovery meant that the interpolated twitch height was not reliable. As a result, this investigation was unable to establish if reductions in voluntary activation after exertion differed significantly to that in healthy participants. If present, abnormally reduced activation after exertion could cause greater physiological fatigue and affect experienced fatigue (Stackhouse et al. 2001; Yamada et al. 2002). Interestingly, several healthy participants demonstrated relatively low levels of voluntary

activation when compared to results in other studies, although there were no significant differences to the PN group, and the reason for this is unclear. Methodological issues such as the timing of the twitch during the MVC or a non-linear relationship between voluntary force and interpolated twitch height could under or overestimate activation, but there is no reason to suggest that these factors would affect the healthy group but not PN participants (Folland and Williams 2007; Shield and Zhou 2004). As activation in PN participants was similar to ranges reported elsewhere, the somewhat lower activation in some healthy participants is more likely to be attributable to previous injuries or reduced motivation. Although all participants were screened for injury, old, benign injuries which are not apparent on screening have been shown to reduce voluntary activation (Rutherford et al. 1986). Alternatively, healthy participants may not have been as motivated as people with PN, or despite standardised protocols, the expectations of the investigator may have altered verbal encouragement and thus performance. This limitation could be partially addressed by using a blinded assessor but as voluntary activation requires maximal effort, individual motivation during the test would still affect activation.

6.5.1. Response to voluntary intermittent muscle activity

Protocol A assessed physiological fatigue in response to intermittent voluntary sub maximal isometric contractions that aimed to mimic functional muscle activity, were practical to perform and allowed maintenance of blood flow (Garssen et al. 2005a; Lindeman et al. 1999; Milner-Brown et al. 1986). The choice of exercise protocol somewhat limits the external validity of these results as it is recognised that closed chain, dynamic exercises are more representative of functional activities. However, recording of accurate and comparable recordings of sEMG during more functional exercise would be difficult as alterations in muscle length and skin position would reduce the reliability of recordings.

During Protocol A, three PN participants stopped exercising as they reported feeling fatigued despite minimal changes in their force production. Two further PN participants became unable to produce forces above 40%, a criterion for stopping the test and they expressed high perceived exertion on the Borg scale (17 and 19). All five participants who failed to complete the protocol reported problematic experienced fatigue (PNF). Nevertheless, their baseline measurements of strength, voluntary activation, and other physiological fatigue tests were similar to healthy and PN participants who completed the protocol. In addition, there was no difference between their performance during the sustained contraction and intermittent electrical stimulation in Protocol B compared with other PN and healthy participants, suggesting that they had normal muscle endurance and fatigability. This suggests that their inability to complete the fatiguing exercise was due to factors other than physiological fatigue. These factors could include enhanced or early perceived exertion and may be secondary to reduced cardiovascular fitness. Alternatively, altered perceived exertion could represent a learnt protective response preventing over exertion before muscular fatigue is detectable, as reported in CFS (Noakes et al. 2005).

The reduced endurance of some PN participants during intermittent voluntary contractions of the knee extensors contrasts with findings from one study in people a mean of seven years after GBS (Dornonville de la Cour and Jakobsen 2005). In their study, 40 participants after GBS demonstrated normal and significantly greater endurance of the wrist and ankle muscles respectively during isokinetic contractions when compared to healthy participants (Dornonville de la Cour and Jakobsen 2005). These conflicting results could be due to differences in the muscle groups tested or the muscle action used to elicit fatigue. Alternatively, the inclusion of people with other, chronic PN in addition to GBS in the current study may mean increased endurance in GBS participants was masked.

Indeed, people with chronic PN could have a different fatigue profile than those after GBS as four of the five participants that did not complete all repetitions in Protocol A had CIDP. Although the small number of participants with CIDP (n=7) makes firm conclusions difficult, it is possible that people with CIDP experience greater or altered fatigue or have reduced tolerance to exercise. People with CIDP reported significantly more severe experienced fatigue in Chapter Five, although again these findings could be an artefact of the sample size and composition as they have not been found by others (Merkies et al. 1999). Boukhris et al. (2005) described 11 cases in which experienced fatigue was the predominant initial symptom of CIDP, although the frequency of fatigue as a presenting symptom of CIDP was not explored (Boukhris et al. 2005). However, it is possible that participants with CIDP were more sensitive to feelings of fatigue and exertion if they perceived that they could precipitate a worsening in their condition. This suggests that both experienced and physiological fatigue should be further investigated in sub-groups of people with different forms of PN.

A limitation of protocol A was that all contractions were performed at a percentage of each individual's maximum force (50%). Whilst this is a commonly used method of testing and training which allows standardisation of work load, everyday tasks demand a greater percentage of MVC for weaker participants than those with normal strength (Shumway-Cook et al. 2002). Therefore some weaker PN participants could experience greater physiological fatigue during daily activities which would not be detected in this study. Future studies could use a standard exercise intensity or fixed external load to make more realistic comparisons between people with weakness due to PN and healthy volunteers. Alternatively, a more functional fatiguing exercise (e.g. repetitive walking or stair climbing) as used by others could be utilised (Schwid et al. 1999). Common fatiguing activities could be identified from patient opinion through surveys, interviews or focus groups to increase the relevance of the physiological tests to every day performance in the wider patient group. Functional fatiguing exercises were not used the current study as it complicated force and EMG activity measurement and, as the response of participants to fatiguing exercise was unknown, may have had safety implications.

Recovery from repeated voluntary muscle contractions has not been reported previously in people with PN but was similar between all participants including those who did not complete all contractions in Protocol A. This implies that the inability to complete all contractions during

Protocol A in some PN participants and the reported worsening of experienced fatigue after exertion (Chapter Five and Merkies et al. 1999) are unlikely to be caused by abnormal recovery of central and peripheral factors of physiological fatigue.

Protocol A produced physiological fatigue in both healthy and PN groups as the final MVC force did not return to pre-fatigue values during the course of the test in either group (mean decline in strength from baseline= H: 63 ± 109 ; PN: 83 ± 42 Newtons). As discussed on Page 190, a decline in available force after fatiguing exercise could have significant negative effects upon functioning in individuals who already have reduced muscle strength as it means that greater effort and/or the use of compensations would be required to undertake even simple activities. As PN participants were significantly weaker they had to utilise a greater percentage of their MVC force to perform activities of daily living. Further loss of strength after exertion could explain the increased severity of experienced fatigue after exercise which was reported by ten PN participants in Chapter Five.

6.5.2. Response to a sustained contraction and intermittent electrical stimulation

By measuring the response to a sustained MVC, Protocol B allowed assessment of the physiological fatigue of the knee extensors whilst minimising the effect of cardiovascular components. The decline in stimulated force after intermittent electrical stimulation allowed direct measurement of the fatigability of the knee extensor muscles.

There were no significant differences between healthy and PN groups during sustained contractions of the knee extensors in Protocol B (Fatigue index (mean \pm SD) = H: $59 \pm 18\%$; PN: $60 \pm 14\%$). These results agree with the findings of Garssen et al. (2005b) in the elbow flexors, who found no significant differences in force decline between healthy volunteers and ten people with severe experienced fatigue after GBS. However, they did find that peripheral fatigue of the elbow flexors developed significantly more slowly in people after GBS, demonstrating increased peripheral endurance in comparison to healthy participants (Garssen et al. 2005b). The findings from reports in other neurological conditions are equivocal. Some have reported a significantly greater force decline during a sustained contraction implying increased fatigability of the ankle dorsiflexors and knee extensors in people with polyneuropathies or CMT, when compared to healthy volunteers (Lindeman et al. 1999; Milner-Brown and Miller 1989). Conversely, in 34 diabetic patients with neuropathic symptoms, increased peripheral endurance was reported in the knee and ankle flexors and extensors, despite significantly reduced strength in comparison to healthy participants (Andersen 1998). They proposed that the diabetic participants had a greater proportion of fatigue resistant muscle fibres, but this was not measured and so could not be proven. In the current study, the fatiguability of the knee extensors was examined using intermittent muscle stimulation. The results indicated that people with PN had similar fatiguability of these muscles to healthy participants, despite being significantly weaker.

A range of factors including the muscle tested, the duration and intensity of the fatiguing exercise, and motivation of participants may account for some of the differences between studies. In particular, unlike participants in Lindeman et al's study (1999) volunteers in the current study did not exercise until exhaustion. Although this may have revealed greater differences between groups it was not feasible for health and safety reasons as participants had to travel home on the same day of testing and the reaction of participants to the testing protocols could not be predicted. Future work could seek to test PN patients to exhaustion if appropriate accommodation and monitoring could be provided although the willingness of people with fatigue to exercise to exhaustion may impede recruitment.

There were no differences in the recovery of healthy and PN groups after the sustained MVC in Protocol B. This contrasts with the only other study which examined recovery after a sustained 60 second MVC in people with neurogenic weakness (Milner-Brown and Miller 1989). They reported a large, initial decline in the sEMG amplitude from the tibialis anterior muscle in 15 participants during recovery contractions after a sustained 60 second MVC, proposing that this was caused by alterations in calcium release from the sarcoplasmic reticulum which delayed recovery (Milner-Brown and Miller 1989). However, markers of sarcoplasmic calcium release, such as response to low frequency stimulation, were not measured in their study, and the range of conditions included make comparisons to other work difficult. The current study is the first to measure low frequency recovery in PN participants. Delayed low frequency recovery (DLFR) appears associated with disuse and inactivity in studies of healthy people (Duchateau and Hainaut 1998) but has been improved by targeted exercise training (Maffiuletti and Martin 2001). In the current study, there were no significant differences in low frequency recovery between PN and healthy groups, implying normal sarcoplasmic reticulum functioning in PN participants, although this can only be confirmed by invasive measurements. Although there was a somewhat larger decrease in 20:100 Hz stimulated force ratio, indicating DLFR, in PNF participants when compared to PNN and healthy groups, this was not statistically significant. Whilst this could indicate that DLFR contributes to experienced fatigue in this participant subgroup the very small sample necessitates further study to determine if this is a factor.

There were also no significant differences between the median frequencies of healthy and PN participants, or between PNF and PNN participants, at the start and end of the sustained MVC. This indicates that the patterns and frequency of muscle activation is largely normal and is similar to findings in people with post polio syndrome (Ng et al. 2004; Sharma et al. 1995). In healthy subjects, median power is shifted towards lower frequencies with fatigue, as larger motor units are recruited and motor units increase firing synchrony (Bigland-Ritchie et al. 1983; Westerblad and Allen 2002). The decline in the median frequency of the power spectra is also thought to reflect a beneficial and normal adaptation to prolonged muscle activity, as the slowed relaxation of muscle requires a lower frequency of stimulation to maintain force (Duchateau and Hainaut 1998). However, unlike healthy volunteers, the decline in median frequency during the MVC was not significant in PN participants in the current study. This is

similar to the findings of others in 86 participants with neuropathic weakness (Yaar and Niles 1992) but the reason for this is unclear. During a sustained MVC, blood flow to the muscle is reduced by the contracting muscle, necessitating anaerobic respiration and slowing the relaxation rate of the muscle so that a lower frequency of stimulation is required to maintain force (Duchateau and Hainaut 1998). However, as PN participants were significantly weaker in the current study, it is possible that their atrophied muscles did not significantly occlude blood flow during the sustained MVC so that some aerobic respiration still took place in the muscles (Behm and St-Pierre 1998; Garssen et al. 2005b). This would minimise anaerobic respiration within the muscles, slow the accumulation of metabolic by-products, maintain the relaxation rate of the muscles and so a smaller change in frequency would be required.

However, this finding could also be explained by changes in motor units after PN and the method used to measure median frequency in this study. In one study of 37 people at least one year after GBS, 60% had enlarged motor units as a result of compensatory reinnervation (Dornonville de la Cour et al. 2005). If PN participants in the current study had enlarged motor units, the sEMG electrodes may have recorded from fewer units and so the recruitment of larger motor units and increased synchrony would not be reflected in their EMG signal. This could result in a somewhat smaller decrease in median power frequency in people with PN when compared to healthy participants, as seen in this study. It is also possible that the wide variability of frequencies seen in the PN group in this study in concert with the small sample meant that the decline in median frequency did not reach statistical significance. Therefore, further work to examine changes in power spectra frequency after fatigue in larger and more homogenous PN cohort is warranted.

This is the first study to directly investigate the fatigability of the knee extensor muscles in response to electrical stimulation in people with PN. The results showed that the response of healthy and PN, and PNN and PNF participants was not significantly different, indicating similar fatigability of muscles (Burke et al. 1973). This is supported by findings in affected muscles in people after polio (Borg et al. 1988) but contrasts with the conclusions of others in people with MS and older people (Ditor and Hicks 2000; Kent-Braun et al. 1997). However, the results cannot be directly compared to other studies as participants in this study completed the sustained MVC prior to measurement. This could have fatigued the knee extensors before being stimulated. This does not affect the comparison between healthy and PN groups in this study, as all participants performed the tests in the same order. However, when the intermittent electrical stimulation was repeated in unfatigued muscles in one PN participant, there was a small (6%) difference indicating that muscles began the electrical stimulation still somewhat fatigued. This limitation could be addressed in future studies by arrangement of an extra testing visit which would allow comparison between results in different patient groups.

6.5.3. Associations between physiological and experienced fatigue and functioning

The work presented here and in Chapter Five demonstrated that measures of physiological fatigue, including sEMG activity and voluntary activation, were not significantly associated with

the severity of experienced fatigue reported by participants with PN. Although the validity of these results is limited by a number of factors including the small, self-selected sample, diverse neuropathies studied and the use of non-functional fatigue tests, the similarity between the physiological fatigue profile of PN and healthy participants suggests that the greater severity of experienced fatigue reported by many people with PN is predominantly caused by other factors.

The results from Chapter Five showed that an increased severity of fatigue was significantly associated with reduced activity levels, poorer mood, increased activity limitations and reduced participation. This could indicate that an increased severity of experienced fatigue is simply a symptom of a more severe PN. However, the lack of association between experienced fatigue and several other impairment measures, including muscle strength and neuromuscular fatigue suggests that the severity of experienced fatigue is independent of disease severity. This is supported by a report from 100 people at least one year after GBS in which experienced fatigue (measured on the FSS) was not significantly associated with the severity of symptoms at nadir, antecedent events or infections (Garssen et al. 2006c). However, neither Garssen et al. (2006) nor the current study has identified clear contributors to more severe experienced fatigue.

Knee extensor strength, activity levels and resting heart rate were significantly reduced when compared to healthy participants (in Chapter Five) and there was a trend for people with PN to report greater exertion during fatiguing exercise. Although these measures were not individually associated with the severity of experienced fatigue, they could still influence experienced fatigue collectively. Decreased muscle strength and reduced cardiovascular fitness (as seen in the current studies when compared to healthy participants) could precipitate a greater perceived exertion when undertaking activities of daily living. This may lead to avoidance of exertion and reduced activity levels (as seen in comparison to healthy participants in Chapter Five). Reduced activity would further decrease cardiovascular fitness, increase muscle weakness and increase feelings of exertion during daily activities resulting in greater experienced fatigue (Sharpe and Wilks 2002). However, the sequence in which these factors could contribute to experienced fatigue is not clear and it is equally possible that greater experienced fatigue has negatively influenced these factors. Nonetheless, the findings of this study indicate that further investigation of activity limitations, cardiovascular fitness, activity levels and perceived exertion in a larger homogeneous group is warranted to determine if they have an association with experienced fatigue.

6.5.4. Limitations

In addition to limitations discussed in context throughout this section and in Chapter Five, the small self-selected sample who volunteered to undergo physiological fatigue tests is likely to have limited external validity to all people with PN. As four participants had undertaken the exercise programme in Chapter Three, although over six months previously, their fatigue profile may have been atypical of the target population. Their data may have biased results as experienced fatigue was significantly reduced after the exercise intervention, and so the

factors which may have contributed to experienced fatigue may have also been largely reduced. Finding PN participants that conformed to the inclusion criteria, could travel for testing and were happy to participate was also difficult. In addition to not meeting the required sample size for this study ($n=16$), this also meant that it was not possible to match healthy and PN participants, decreasing the strength of comparisons between groups.

As discussed in Chapter Five, the investigator was not blind to diagnosis, placing the results at risk of bias. Although instructions and verbal encouragement were standardised to avoid bias, it is possible that the expectations of the investigator influenced the results. Another possible limitation is that it was assumed that the physiological fatigue profile of the healthy group was normal and so could be used to compare and identify any abnormalities in the PN group. However, as the fatigue protocols were adapted for this study and other investigations have not examined the same factors, used similar methods or have tested very different participants (e.g. athletes or the elderly) it is not possible to conclusively establish the normality of the results of the healthy group.

6.6. Conclusions

This study was the first to investigate many aspects of physiological fatigue in people with inflammatory PN.

Although these findings and those from Chapter Five require confirmation in a larger study, they imply that experienced fatigue in participants with PN is not associated with abnormal physiological fatigue of the knee extensors. Although these muscles were significantly weaker than healthy participants, they demonstrated similar levels of voluntary activation, fatigue and recovery during testing. This suggests that the factors that produced muscle weakness in people with PN did not precipitate an altered physiological fatigue profile.

Interestingly, several people with PN who complained of severe experienced fatigue did not complete the voluntary fatigue protocol (Protocol A) despite no significant differences to other people with PN or healthy participants on other tests of physiological fatigue. Their early cessation of muscle work may be attributable to a learnt protective response to avoid over exertion to limit worsening of fatigue and warrants further investigation. Although not significantly associated with experienced fatigue, cardiovascular fitness and strength were significantly reduced in people with PN when compared to healthy participants. Whilst the relevance of this finding is unclear, it could suggest that these factors could indirectly influence experienced fatigue and that they should be re-examined in future work.

It is also recommended that future studies examine the response to a functional fatiguing protocol (e.g. stair climbing) and utilise a larger sample to ensure adequate statistical power and so that comparisons between diagnostic groups in PN and between people with and without severe experienced fatigue can be made.

Chapter 7. Conclusions

7.1. Aims and Objective

The overall objective of this thesis was to examine the role of exercise for treating people with PN. Two aims were developed. These were to:

- (i) Evaluate the practicality and possible effects of a community based exercise intervention for people at least 12 months after the nadir of GBS and with stable CIDP.
- (ii) Investigate and describe the nature of fatigue in people with inflammatory PN.

To fulfil these aims, it was also necessary to evaluate outcome tools which could accurately and comprehensively describe aspects of functioning.

7.2. Summary of findings

Persistent problems, including weakness, altered sensation, pain and fatigue are common in inflammatory PN and contribute to poor health status and reduced functioning (de Jager and Minderhoud 1991; Lennon et al. 1993). Exercise would be an attractive self-management choice for many people with PN if it could be shown to be practical and beneficial to functioning. However, there is little evidence to support its use in people with PN (White et al. 2007a). The prospective, uncontrolled study described in Chapter Two demonstrated that PN participants can undertake an individually tailored exercise intervention safely and independently in the community. Significant improvements in activity limitations, physical functioning, mood and fatigue apparent after the intervention remained significantly improved at six months follow up, except for depression. In addition the majority of PN participants reported continuing to exercise at six months. Whilst this report is likely to have been influenced by recall bias and the desire to please the rater, it suggests that some participants successfully underwent changes in their health behaviour that may reduce their risk of health complications associated with a sedentary lifestyle. The absence of a non-exercising patient control group, lack of rater blinding, reliance upon self report to indicate exercise adherence and the small sample of volunteers mean it is not possible to attribute the changes after the intervention to the intervention itself and reduces the external validity of the findings. However, the findings demonstrate that prescribed unsupervised community based exercise is practical and well tolerated by people with PN. The experience of conducting this study therefore informs the recommendations for a future multi-centred randomised controlled trial to evaluate the effects of exercise in people with inflammatory PN that is discussed below.

During their use in Chapter Two, it became apparent that some outcome tools were not appropriate or responsive to measure changes after the exercise intervention. The primary outcome tool, the ODSS questionnaire, had a ceiling effect and so was insensitive to minor lower limb activity limitations such as the ability to run or climb stairs. This meant that it did not reflect small but potentially relevant changes in lower limb functioning. A new tool, the overall

neuropathy limitations scale (ONLS) was developed to address the shortcomings of the ODSS and was evaluated in Chapter Three. The ONLS is very similar to the ODSS but it includes an item regarding running and climbing stairs in addition to walking items. The clearer instructions and expanded lower limb criteria provide greater face validity than the ODSS and the ONLS is able to detect difficulties in running and stair climbing, in addition to walking, thereby reducing the undesirable ceiling effect of the ODSS. However, the ONLS was somewhat less responsive than the ODSS in the current study. Whilst this may be an artefact of the sample used, in terms of both size ($n=17$) and composition, it indicates that neither the ODSS nor ONLS can be currently recommended to be used to measure changes in activity limitations in future interventions.

Reduced mobility due to residual deficits in inflammatory PN may be improved by exercise interventions (Bernsen et al. 2005; Erdmann et al. 2005; Lennon et al. 1993; Pearson et al. 2004) but, other than the ten metre walk test which was not responsive to changes after the exercise intervention in Chapter Two, no outcome tools which specifically measure ambulant mobility have been evaluated in people with PN. Therefore, three tools were investigated in Chapter Four. These were the Walk-12 (a 12 item questionnaire scored on a five point Likert scale), and the standard and modified physiological cost index (PCI and mPCI, measured during walking at a preferred pace on a flat surface). The Walk-12 and mPCI were shown to be reliable and valid. The mPCI was also responsive to improvements after the exercise intervention. However, the PCI was not reliable and did not significantly correlate with the criterion measure of oxygen cost in healthy or PN participants, suggesting it had limited validity. Further work is required to establish the responsiveness of the Walk-12, to confirm the properties of the mPCI in a larger sample of PN participants and to determine if the Walk-12 is superior to other common mobility tools which are used in other conditions. Nevertheless, the studies in Chapter Four show that the Walk-12 and mPCI measured walking ability appropriately and are potentially useful tools for people with inflammatory PN, in both clinical and research settings.

The second aim of this thesis was to describe the nature and possible contributors to experienced fatigue which is a significant problem for many people with inflammatory PN (Bernsen et al. 2002; Merkies et al. 1999). Studies to investigate and describe the potential factors which were associated with experienced fatigue in people with PN were presented in Chapters Five and Six. This is the first investigation of the relationship between experienced and physiological fatigue and wider functioning, including the energy cost of walking and activity levels, in people with PN. The results of this study were limited by the small, self-selected sample but the findings confirm that people with PN exhibited greater levels of experienced fatigue than healthy people, which agrees with reports by others (Merkies et al. 1999). Experienced fatigue was significantly associated with increased activity limitations, poorer mood, lower activity levels and reduced physical and social functioning, but the cross-sectional design of the study meant that it was not possible to determine if these factors contributed to, or were the result of experienced fatigue. Measures of muscular endurance

(physiological fatigue) were not associated with experienced fatigue but cardiovascular fitness and knee extensor strength were significantly reduced when compared to healthy participants. Whilst these factors were not significantly associated with increased experienced fatigue their potential relationship with experienced fatigue in people with PN is worthy of further investigation.

7.3. Clinical implications

The findings of the fatigue and exercise studies need to be established in larger groups of participants in blinded and controlled trials before they can be categorically proven. However, in the absence of controlled clinical trials, clinical practice has to be based upon the best observational studies available (Evans 2003). Therefore, major implications for clinical practice arising from the findings of this thesis are discussed here.

7.3.1. Exercise

The results of the study of a community based exercise intervention indicate that a prescribed, combined aerobic, strength and functional exercise intervention could be offered to people with inflammatory PN, to facilitate safe exercise. Participants were able to exercise independently in the community following clinical assessment, orthotic prescription where appropriate and individual exercise prescription. The side effects were mild and similar to those described by others in 18 people with CIDP or after GBS and in 14 participants with chronic PN after exercise interventions (Garssen et al. 2006a; Ruhland 1997). The findings of significantly reduced activity limitations, improved experienced fatigue and strength support the results of others (Garssen et al. 2006a; Ruhland 1997), but the design of the study meant that these changes could not be attributed to exercise.

The design of a suggested potential exercise programme to improve functioning and fatigue, informed by the exercise study is shown in Appendix Six. This programme includes aerobic and functional components in addition to dynamic strengthening exercises. Several of the outcome tools identified in this thesis could also be used to provide appropriate and suitable indicators of the effect of interventions in clinical practice, although it is noted that a tool's performance in a group does not necessarily mean it is equally suitable for monitoring change in individuals (Hobart 1996).

7.3.2. Fatigue

This study found that experienced fatigue is a persistent and severe problem and is associated with increased activity limitations for many people with PN, which agrees with the findings of others (Merkies et al. 1999). Therefore, clinicians should be encouraged to ask patients with PN about the presence and nature of any fatigue and use a fatigue questionnaire in their clinical assessment if they suspect fatigue to be present. The fatigue impact scale (FIS) or the fatigue severity scale (FSS) could be used to assess experienced fatigue in a clinical setting. Although the FSS has been validated in PN, the FIS might describe fatigue more fully as, unlike the FSS, it can quantify the effect of experienced fatigue on physical, cognitive and

social function (Fisk et al. 1994). However, the properties of the FIS, including responsiveness, require investigation in people with PN.

7.4. Implications for future research

7.4.1. Patient and public involvement

The absence of patient or user involvement in the design of the studies in this thesis is a key limitation to their findings. Patient and public (or partner) involvement (PPI) can help develop research priorities, generate relevant research questions and it is considered to be vital at each stage of research; from design to outcome dissemination, to ensure that the study addresses questions that are meaningful to patients and particularly for complex interventions such as exercise (Medical Research Council 2008). Therefore, future studies should seek to involve patients in all aspects of the research process at the earliest opportunity; this may include utilising existing patient organisations such as the Guillain Barré Syndrome Support Group (GBSSG) to guide research priorities, inform trial design and disseminate findings but could also include local patients and their carers in project steering groups and informal networks (INVOLVE 2012).

7.4.2. Design of a future randomised controlled trial of exercise to determine the effects of exercise in people with inflammatory PN

The design of the investigation of exercise in Chapter Two aimed to mimic a typical clinical exercise intervention for people with inflammatory PN but its uncontrolled, unblinded design and small number of participants meant that it was unable to establish the effects of the intervention. However, information and data from the study in Chapter Two should be used to design a future RCT with secure concealment of group allocation and blinded assessors to minimise selection and observer bias.

Sample

An appropriate sample size based on a pre-determined power and level of significance to detect a clinically meaningful difference in the primary outcome and taking account of the standard deviation of the measure could be calculated from the data in Chapter Two. This is likely to reveal a sample size in excess of the numbers recruited in Chapter Two, therefore a multi-centred design is recommended. Whilst this design could facilitate recruitment of a wider range of PNs and include ambulant and non-ambulant participants, this would increase heterogeneity and necessitate a much larger sample. It may therefore be preferable to develop separate studies to investigate the effectiveness of exercise in different forms of PN and in non-ambulant participants.

Control

Randomisation to a control group of usual care rather than exercise might not be acceptable to some potential volunteers, increasing attrition. A delayed intervention control group, whilst ethically acceptable given the current lack of evidence for the efficacy of exercise to reduce

activity limitation in people with PN, is likely to be more acceptable to potential participants and so increase recruitment to the study. However, it is also likely to either significantly increase the length of the study or reduce the possibility for long term follow up of control and intervention groups. Studies investigating exercise in other conditions including stroke and chronic fatigue syndrome have overcome this by using control interventions such as advice and education or, more pragmatically, usual care (Saunders et al. 2009; Wallman et al. 2004). However, these are unlikely to control for the effects of the increased time and attention given to the experimental group, therefore an alternative intervention such as relaxation may be more appropriate in a future trial.

Intervention and outcome measurement

The exercise programme provided to participants in Chapter Two appeared practical and well tolerated but did not include overt components of education or interventions to facilitate a change in health behaviours. Whilst beliefs about exercise and perceived barriers to physical activity have not been investigated in PN changing health behaviours and addressing fear avoidance has been purported to be a vital element of interventions to increase physical activity (Nijs et al. 2013). Therefore, exploration of health beliefs and addressing health behaviours could be included in a future exercise intervention in people with PN and could include aspects of motivational interviewing, cognitive behavioural based therapies, counselling and advice and education (Nijs et al. 2013).

The ONLS and ODSS did not appear entirely suitable to use as a primary outcome tool in a future exercise trial. However, further research is needed to determine if the responsiveness of the ONLS is improved in a larger sample or to alter the scoring criteria so that stair climbing and running are scored separately. Other work should investigate if different tools (such as the R-ODS) demonstrate better responsiveness to the ODSS or ONLS and utilise patient views in tool selection to ensure that the outcomes are relevant and meaningful to the target population (INVOLVE 2012). In the absence of these data, the SF-36, which was responsive to changes after the exercise intervention and is valid in people with PN, is proposed as the primary outcome in a future trial of exercise (Merkies et al. 2002c). The SF-36 can provide comprehensive data on functioning as items cover a range of routine activities which are of importance to patients. Subscale scores can also be compared to normative values which make them easily interpretable. Secondary outcomes could include the Walk-12 and mPCI, if their properties can be established in further investigations, as mobility is of great importance to patients and prominently affected after GBS and in CIDP (Chiou and Burnett 1985; Erdmann et al. 2005; Forsberg et al. 2004).

Assessment of adherence to the exercise programme should also be objectively measured, but methods of recording need to be simple and reliable. The heart rate monitors were not used reliably to record heart rate in Chapter Two whilst the activity monitors used in Chapter Five are reliant on the participant remembering to wear them and cannot provide direct indications of the intensity of exercise. As no single measure appears entirely suitable to

measure adherence, it is suggested that future studies use a combination of activity monitoring and self-report exercise diaries.

The health beliefs and opinions about exercise of people with PN were not investigated in Chapter Two. A mixed methods design would allow qualitative data from a sub-set of participant interviews or focus groups to be generated in addition to quantitative measurement in a future trial of exercise. Whilst not allowing direct comparison within or between groups, qualitative methods provide rich contextual data that can complement quantitative outcomes and would inform further work and clinical practice (Sim and Wright 2000).

The study in Chapter Two did not overtly target or measure self efficacy, described as the confidence someone has in their ability to perform a specific activity or alter a behaviour (McAuley 1993). A future study could investigate whether any changes in exercise are mediated by self-efficacy using qualitative methods such as interviews or measured using standardised tools such as the self-efficacy for exercise scale to allow statistical comparison to controls and to indicate the magnitude of any change (Fletcher and Banasik 2001).

Cost effectiveness was also not measured in Chapter Two. These data would inform health care providers about the costs of the intervention and its relative benefit, influencing the wider, clinical provision of exercise for people with inflammatory PN, and so should be measured in a future trial. There are several measures of cost effectiveness but the Quality-Adjusted Life-Year (QALY) is the most widely used (Roine et al. 2009). Measurement of QALYs derived from data obtained from participant interviews regarding overall health, social and informal service use and costs in a future study of exercise would also allow comparison to other interventions and so inform service delivery and wider health policy (Roine et al. 2009).

7.4.3. Fatigue

The studies in Chapters Five and Six failed to establish clear contributors to the fatigue experienced by people with PN. Abnormal physiological fatigue was not apparent in people with PN using a standardised protocol of repetitive sub-maximal voluntary isometric contractions. However, it is possible that this protocol may not have adequately mimicked functional activity and so physiological fatigue brought on by everyday functional muscle activity may have been missed. Future work should therefore seek to develop a functional task for participants to perform until fatigue, to facilitate further investigation of physiological fatigue.

A key limitation of the work in Chapter Five was that the tools used to indicate experienced fatigue were not originally developed for people with PN and constrained their answers to pre-determined categories. This may have limited their description of their fatigue and so restricted our understanding of this complex symptom. Future work could use qualitative methods and/or seek to develop new outcome tools with PPI to increase our understanding of fatigue and improve the available methods to capture these data.

Although the size of the sample in the fatigue investigations in Chapters Five and Six was informed by other studies, the wide variability in participant characteristics which was evident meant that any future work should utilise a larger sample to increase external validity. Future

work could also examine psychological, immune and endocrine factors which may contribute to fatigue but which were beyond the scope of the current study.

Appendix 1 Steering Group details

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Dear Examiners

This letter is to confirm that the choice of outcome measures utilised in Chapter 2 of this thesis were pre-determined by an initial steering group for the prospective, single blind uncontrolled study of the effect of exercise in inflammatory neuropathy.

The initial steering group met in 2001 and Rachel Stockley (née Graham) was subsequently successful in being awarded a Guy's and St Thomas' Charity PhD studentship award in to work on this study which formed part of her PhD studies.

The steering group comprised:

Professor R.A.C Hughes: Professor of Neurology, Guy's and King's College Foundation Hospital Trusts and Neuroinflammation Research Group, School of Medicine, King's College London,

Professor D.J. Newham: Head of Division of Applied Biomedical Research, King's College London,

Professor L. Turner-Stokes: Dunhill Professor of Neurorehabilitation, King's College London and Director of Regional Rehabilitation Unit, Northwick Park Hospital, Middlesex.

Professor J.A. Weinman: Professor of Psychology as Applied to Medicine, Institute of Psychiatry, King's College London,

Dr C.M. White: Applied Biomedical Research Division, King's College London.

Yours sincerely

Claire White: MSc, PhD, MCSP.

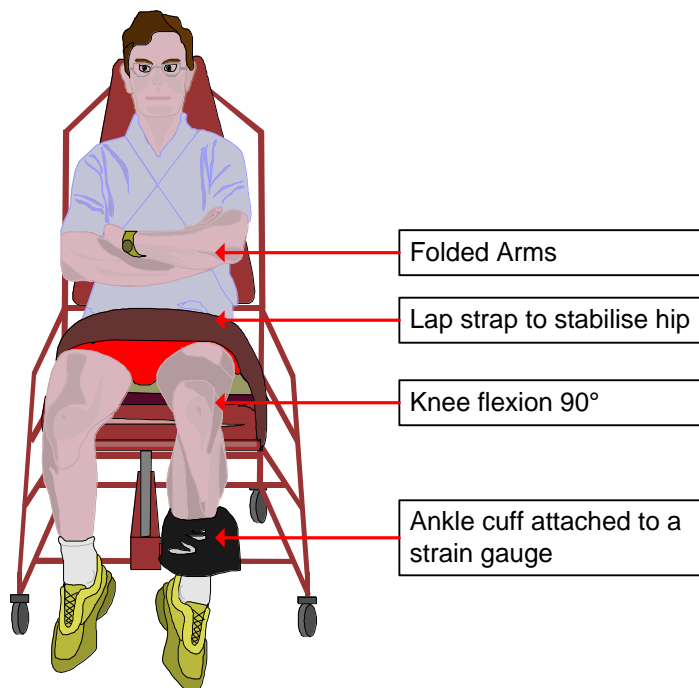
Appendix 2 Method of measuring knee extensor force in Chapter Two

Participants were positioned as shown in Figure 1 below.

The seat was adjusted so that the knee was flexed to 90° and they were secured with lap straps to provide proximal stability. A padded cuff connected to a strain gauge was positioned above the medial and lateral malleoli of the ankle. Participants were instructed to fold their arms to prevent isometric upper limb work (American College of Sports Medicine 1995). After a brief warm up of several sub-maximal contractions, each participant performed three maximal consecutive contractions (Lord et al. 1992). If force production continued to increase on the third contraction, more measurements were taken until force did not increase further to ensure adequate familiarisation.

Participants were instructed to straighten their knee maximally and given vigorous, standardised verbal encouragement throughout (McNair et al. 1996; van der Ploeg and Oosterhuis 1991). They were provided with simultaneous visual feedback, as a small pilot study, confirmed by the work of others (Ogiwara et al. 1991), demonstrated greater force production in three out of four healthy participants when they could see their progress (410.5 ± 80.9 Newtons) in comparison to when they could not (394.3 ± 64.1 Newtons). The linear force produced was amplified ($\times 25$), passed through an analogue to digital converter (1401, Cambridge Electronic Design) and displayed visually using Signal software (Signal version 2.1 Cambridge Electronic Design).

Figure 1 Position for isometric knee extension testing using fixed dynamometry



Appendix 3 Instructions for scoring the Overall Neuropathy Limitations Scale (ONLS)

Introduction

This questionnaire should be administered in a comfortable and quiet room. The patient should sit.

Start by saying “I would like to ask you about some activities you may do every day. This is to help us understand any difficulties you might have. Please answer each question as accurately as you can and ask me to repeat a question or slow down if you do not understand”.

Encourage the patient to answer all the questions themselves. A carer, relative or friend may help if the patient is unsure or has communication difficulties. If the patient does not understand, change the question to, “**Do you have difficulty doing - activity x - ?**”. Give clear instructions and, if necessary, demonstrate the task required. Ask about the tasks in relation to their usual activity at present. If their condition has changed recently, ask them to base their answers on the last 24 hours.

In judging whether tasks are prevented, allow aids, but not aid from another person.

This questionnaire assesses the limitations whatever the medical reason. If the patient has other conditions which cause limitations, this is recorded in the last question.

Upper limb items

Ask about the upper limbs first.

Does the patient have any symptoms in their hands or arms e.g. tingling or weakness?

Ask: Do you have any tingling, numbness, pain or weakness in your hands or arms?

Include all symptoms that are attributable to peripheral nerve conditions, including carpal tunnel syndrome and neuropathic pain. Do not include symptoms not due to peripheral nerve disease e.g. arthritis, but if such symptoms affect function, check the ‘yes’ box at the foot of the page.

Washing and brushing hair

Ask: Is your ability to wash and brush your hair affected?

If the patient considers themselves to be affected, ask: **Are you able to wash and brush your hair?**

If they cannot wash **and** brush their hair the task is prevented. Only being able to do one or the other is not sufficient, and the task should be considered prevented. If a patient does not usually wash or brush their hair, they should be asked if they think they could, if required. If there is doubt, ask the patient to mime the tasks.

Turning a key in the lock

Ask: Is your ability to turn a key in a lock affected?

If the patient considers themselves to be affected, ask: **Are you able to turn a key in a lock?**

Ask the patient to consider a lock they commonly use at home e.g. their front door. To complete the activity successfully they must be able to turn the lock sufficiently to unlock or lock a door. If they can complete the activity but have difficulty, the task is affected. If they are unable to turn a key in the lock with either or both hands, the activity is considered prevented. If a key turner is used the task should be considered affected. If the patient cannot turn the key in the lock even when using a key turner the task is considered prevented.

Using a knife and fork together (or spoon if knife and fork are not usually used)

Ask: Is your ability to use a knife and fork (or spoon) together affected?

If the patient considers themselves to be affected they should be asked: **Are you able to use a knife and fork (or spoon) together?**

If patients do not use a knife and fork, their usual eating implements should be substituted (e.g. chopsticks). The task is considered as affected if the patient can use cutlery to eat their food but has difficulty. The activity is prevented if the patient cannot use their cutlery to eat. If adapted cutlery is used the task should be considered affected. If the patient cannot use a knife and fork (or spoon) even when using adapted cutlery, the task is prevented.

Do or undo buttons or zips

Ask: Is your ability to do and undo all your buttons and zips affected?

If the patient considers themselves to be affected they should be asked: **Are you able to do and undo all your buttons and zips?**

They must be able to fasten **and** unfasten **all** buttons **and** zips without difficulty to be considered unaffected. If the patient can do and undo all buttons and zips but has difficulty, they should be considered as affected in this task. If they are not able to do and undo all zips and buttons, the activity is considered as prevented. If button hooks and adapted zips are used the task should be considered affected. If the patient cannot fasten or unfasten buttons or zips even when using button hooks or adapted zips the task is prevented.

Dress the upper part of their body excluding buttons or zip.

Ask: Is your ability to dress the upper half of your body (e.g. putting on a T-shirt or jumper) affected?

If the patient considers themselves to be affected, ask: **Are you able to dress the upper half of your body?**

If they can manage to dress but find it difficult, the activity is affected, if they are unable to dress the upper part of the body the task is considered prevented. This activity does not include fastening buttons or zips.

Purposeful movement:

Ask: Can you move either hand or arm at all?

If necessary, ask the patient to show you the movement. Score “yes” if any voluntary movement is observed. Only assess this if all four tasks are prevented. If the patient is not prevented in all the previous tasks, the “not applicable” box should be checked.

ARM GRADE: Work out the score from the answers to the questions using the scoring criteria.

Lower limb items

Does the patient have difficulty running or climbing stairs?

Ask: Do you have difficulty running or climbing stairs?

If they do have difficulty, ask: Are you able to run or climb stairs?

They should be considered to have difficulty with running and climbing stairs if they have difficulty with either. If the patient is not accustomed to running or does not know if running is affected, rely on the answer about stair climbing.

Does the patient have difficulty with walking?

Ask: Do you have difficulty walking?

Difficulty walking may include pain, difficulty walking longer distances, fatigue or unsteadiness.

Does their gait look abnormal?

Ask the patient to walk or mobilise over at least 10 metres at their preferred pace and with their preferred aid. Abnormalities may include altered speed or cadence, foot drop, Trendelenberg type gait, limp, unsteadiness, or inability to maintain a straight direction of movement.

How do they mobilise for 10 metres?

Ask: Would you usually need a walking aid or someone to help you to walk about 10 metres/33 feet?

If the patient uses different aids depending upon the environment they are in, they should be asked which aid they usually use for this distance. If still unsure, the aid used during observation of the last item should be taken. Moderate assistance from one person holding the patient’s arm or hand is considered as unilateral support.

Wheelchair users

If a patient needs a wheelchair to mobilise 10 metres the next two items should be assessed.

Can they stand and walk 1 metre with the help of one person?

Ask: Can you stand up and walk about 1 metre if one person helps you?

This can be answered by the patient or their carer. If the answer is unclear, observe the task. If more than one assistant is required or the patient is unable to walk 1 metre please check the “No” box.

If they cannot walk are they able to make some purposeful movements with their legs?

This should only be assessed if unable to walk 1 metre with the help of one person.

Ask: Can you move either leg or foot at all?

If necessary, ask the patient to show you the movement. Score "yes" if any voluntary movement is observed.

Does the patient use ankle foot orthoses or braces?

Please circle any devices the patient usually wears and the side on which they are usually worn.

LEG GRADE: Work out the score from the answers to the questions using the scoring criteria

Is there any disorder, other than peripheral neuropathy, which affects the above functions?

If the patient does not have any other disorders affecting the upper or lower limb, the 'no' box should be checked.

TOTAL SCORE: Add the arm and leg scores and record the total (out of 12)

Appendix 4 Validity and Reliability of the Cortex Metamax Indirect calorimetry system

Background

The properties of the MetaMax system have not been investigated at work rates analogous to walking. In order to have confidence in the measurement of the criterion indicator of energy cost for the studies in Chapter Four, its validity and reliability must be confirmed.

Aim

The aim of this study was to determine the validity and reliability of measurements of oxygen consumption by the Metamax indirect calorimetry system at heart rates analogous to those attained whilst walking.

Method

Four healthy participants with no cardiovascular, respiratory, neurological or musculoskeletal conditions were recruited to this cross sectional study and consented to complete two sub maximal exercise tests at least 24 hours apart. The testing protocol was designed to allow measurement of heart rates similar to those that may be reached during walking in healthy volunteers and in people with difficulties walking. Participants were asked to avoid strenuous exercise and to refrain from eating for at least two hours before testing.

Participants were fitted with a heart rate monitor (Polar, Finland) and Cortex Metamax 3B (Biophysik, Leipzig, Germany) gas measurement system, consisting of a snug fitting face mask and lightweight (weighing approximately 200 grams) telemetric recording device, worn over the shoulders, shown in Figure 2.

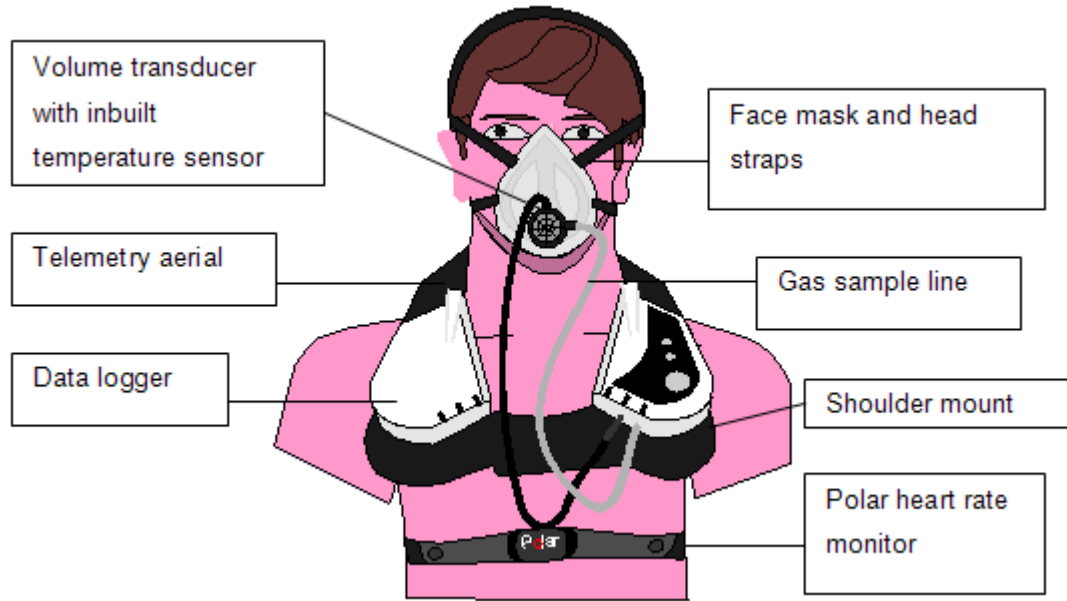
Values of VO_2 from the Metamax were compared to a static system consisting of Servomex fast response oxygen and carbon dioxide analysers, (series 1400; Servomex, Jarvis Brook, Sussex, UK) a dry gas meter (Harvard Apparatus, Kent, UK), mixing chamber, mouthpiece and nose clip. The gases were dried using anhydrous calcium sulphate before analysis.

Participants performed a sub maximal exercise test on a recumbent bicycle ergometer whilst measurements were taken using a heart rate monitor and either the Metamax or Servomex system. Participants were instructed to pedal at 60 revolutions per minute in time with an electronic metronome. Each participant exercised at two stages (50 and 100 Watts) for four minutes, after an initial resting period and warm up (two minutes duration at 25 Watts). A brief warm down concluded the test. The test was repeated using the alternate system (Metamax or Servomex) at least 24 hours after the initial session. Experimental conditions were kept as consistent as possible across the two testing sessions.

On the Servomex system, the volume and percentage of oxygen (O_2) and carbon dioxide (CO_2) in expired gas were manually recorded every 30 seconds, along with heart rate. Data

from the Metamax were displayed on a laptop computer using Metasoft software (version 1.11.5, Cortex, Germany) which provided breath by breath analysis of VO_2 and heart rate.

Figure 2 Diagram to show the Metamax system



After testing, oxygen uptake at standard temperature, pressure and dry conditions (STPD) was calculated for data obtained from the Servomex using the following equations:

$$\text{VO}_2 \text{ (ATPS)} = \text{VI} (\text{F}_\text{I}\text{O}_2 - \text{F}_\text{E}\text{O}_2) \times \left(\frac{\text{F}_\text{I}\text{N}_2}{\text{F}_\text{E}\text{N}_2} \right)$$

$$\text{VO}_2 \text{ (STPD)} = \text{VO}_2 \text{ (ATPS)} \times \left[\left(\text{P}_\text{B} - \frac{\text{P}_{\text{H}_2\text{O}}}{760} \right) \times \left(\frac{273}{273 + \text{T}_\text{r}} \right) \right]$$

The Metasoft software does not display values of expired O_2 or CO_2 , therefore it was not possible to manually calculate VO_2 . However, VO_2 in ambient conditions is calculated by the Metamax system using:

$$\text{VO}_2 \text{ (ATPS)} = (\text{F}_\text{I}\text{O}_2 \times \text{VI}) - (\text{F}_\text{E}\text{O}_2 \times \text{VE})$$

It is then converted to standard conditions using a conversion factor:

$$\text{VO}_2 \text{ (STPD)} = \text{VO}_2 \text{ (ATPS)} \times \left[\frac{273}{\text{T}_\text{b} \times \left(\frac{\text{P}_{\text{H}_2\text{O}}}{101.3} \right)} \right]$$

Where VO_2 =oxygen consumption, ml min^{-1} ; ATPS = ambient temperature pressure and saturation; V_I = volume of inspired air, ml; $\text{F}_\text{I}\text{O}_2$ = Fraction of inspired oxygen, (0.209); $\text{F}_\text{E}\text{O}_2$ = Fraction of expired oxygen; $\text{F}_\text{I}\text{N}_2$ = Fraction of inspired nitrogen, (0.79 in room air); $\text{F}_\text{E}\text{N}_2$ = Fraction of expired nitrogen; P_B = Barometric pressure, mmHg; $\text{P}_{\text{H}_2\text{O}}$ = saturation of water in room air (room temperature x room humidity,

mmHg for Servomex, Pascals for Metamax), mmHg; Tr = Room temperature (centigrade), Tb = expiratory gas temperature (Kelvin).

Values of oxygen consumption were normalised to body weight to yield VO₂ measurements in ml kg⁻¹ min⁻¹ for both systems.

Calibration

Both systems were calibrated before every test session.

The Metamax was calibrated according to the manufacturer's instructions, using room air and O₂ and CO₂ concentrations of 17% and 5% respectively. The accuracy of O₂ and CO₂ measurements by the Metamax were also checked with 100% nitrogen and room air.

The Servomex gas analysers were zeroed manually using 100% nitrogen, then calibrated with known concentrations of O₂ (13.69%) and CO₂ (5.03%), before confirming values of room air.

Volume measurement for both systems was calibrated using three and one litre gas syringes.

Data treatment

Metamax: Raw breath by breath values for VO₂ from the Metamax system were averaged over the fourth minute for each stage, to ensure participants had reached steady state (Wasserman et al. 1999). Heart rate was recorded from the fourth minute for each stage.

Servomex: Values for volume and heart rate were recorded from the fourth minute from each stage. Values for O₂ and CO₂ were measured exactly one minute later, to allow for the time lag caused by mixing of the gases in the mixing box.

Analysis

Due to the small sample size, descriptive statistics were primarily used to describe differences in VO₂ data. However, a paired, two tailed t-test was used to determine any systematic differences in VO₂ between readings from the Servomex and Metamax (significance set at p<0.05).

Bland Altman techniques were used to examine agreement between the two systems (Altman and Bland 1983). Limits of agreement were calculated using the following formula:

$$95\% \text{ Limits of agreement} = \text{Mean}_{(x-y)} \pm 1.796 \times \text{SD}_{(x-y)}$$

where x = Metamax measurement y = Servomex measurement (Altman and Bland 1983). As the sample size was small, the value from the t distribution at 95% was used (1.796).

Results

Four healthy participants (three males) completed testing on two occasions (mean age: 37 ± 6 years; weight: 73.3 ± 6.7 Kg).

Calibration

Values of O_2 and CO_2 recorded by the Metamax in room air and with 100% nitrogen were reliable (coefficient of variation: $<1\%$ for all readings before and after exercise). Thirty repeated readings of volumes by the Metamax from three (mean: 3.01 ± 0.04 Litres) and one litre (1.05 ± 0.04) gas syringes and by the Servomex (2.9 ± 0.08 ; 0.98 ± 0.1) were also accurate and reliable.

Validity

There were no significant differences in VO_2 readings from the Servomex and Metamax systems. The 95% limits of agreement indicated that measurements on the different systems varied only slightly (-3.8 to 5.8 ml kg^{-1} min^{-1} , Table 7-1).

Table 7-1 VO_2 and heart rate measurements at rest and during exercise on Servomex and Metamax systems

Stage	VO_2 Servomex (ml kg^{-1} min^{-1})	Heart rate Servomex (beats min^{-1})	VO_2 Metamax (ml kg^{-1} min^{-1})	Heart rate Metamax (beats min^{-1})
Rest	3.46 ± 0.33	71 ± 6	3.03 ± 1.28	77 ± 14
50 Watts	12.1 ± 0.81	103 ± 16	11.17 ± 2.6	105 ± 16
100 Watts	18.9 ± 1.54	125 ± 22	17.3 ± 4.03	129 ± 23

All values are mean \pm SD.

Heart rates were broadly similar during tests, indicating that participants were working equivalently when being measured by both systems (Table 7-1). The mean difference between the two systems was small (1.02 ± 2.7 ml kg^{-1} min^{-1}) and was equivalent to 9.3% of the overall mean VO_2 value. The greatest difference between measurements was at rest, where mean values of VO_2 differed by 13%.

Discussion

The advent of telemetric indirect calorimetry systems allows participants to move freely while data are collected. In addition to increased flexibility, the Metamax system facilitates monitoring of participants in situations akin to those experienced in daily living, including walking. No studies have examined the validity of the VO_2 readings produced by the Metamax at heart rates similar to those attained whilst walking. In this study, conditions were controlled to produce values of VO_2 in four healthy volunteers similar to those reported during comfortable walking in healthy people and people with physical impairments ($12 \text{ ml kg}^{-1} \text{ min}^{-1}$ to $17 \text{ ml kg}^{-1} \text{ min}^{-1}$) (Ijzerman et al. 1999; Waters and Mulroy 1999) to allow validation of the Metamax system.

The Metamax appeared valid as there were no systematic differences in VO_2 values between the Metamax and the standard Servomex system. Oxygen consumption values varied by a mean of 9.3% overall when measured on the Metamax and Servomex. However, day to day variation in VO_2 may account for over 4% of the inconsistency seen between the repeated measurements (Becque et al. 1993). If day to day differences were assumed to contribute 4% variability to the VO_2 values in this study, the Metamax VO_2 measurements would be within 5.3% ($0.58 \text{ ml kg}^{-1} \text{ min}^{-1}$) of the Servomex values. Although small, this variability should be considered when interpreting results of oxygen cost.

A significant limitation of this investigation is the small sample used as only four, healthy participants were included. This considerably limits the external validity of these findings. As heart rate ranges were similar to those reported during walking, the conclusion that the Metamax system appears valid to measure VO_2 within the heart rate range investigated in this study (77 to $129 \text{ beats min}^{-1}$), and for values of VO_2 from $3.0 \text{ ml kg}^{-1} \text{ min}^{-1}$ to $17 \text{ ml kg}^{-1} \text{ min}^{-1}$ may be legitimate.

Conclusion

Measurements of VO_2 recorded by the Metamax appear to have acceptable validity for the range likely to be obtained while walking, although the small sample size limits the strength of this study. Values varied by over 9% between Metamax and Servomex systems, indicating that there is not complete agreement between the two systems. Although this could be attributable to day to day variation in energy consumption as heart rate values were not identical on subsequent testing sessions, it should be considered when viewing data from the Metamax system.

Although future work should be undertaken to conclusively establish the validity and reliability of the system using a larger number of participants, from these results it appears reasonable to use the Metamax to measure oxygen consumption in the studies in this thesis.

Appendix 5 Test re-test reliability of the Kin Com Dynamometer

Method

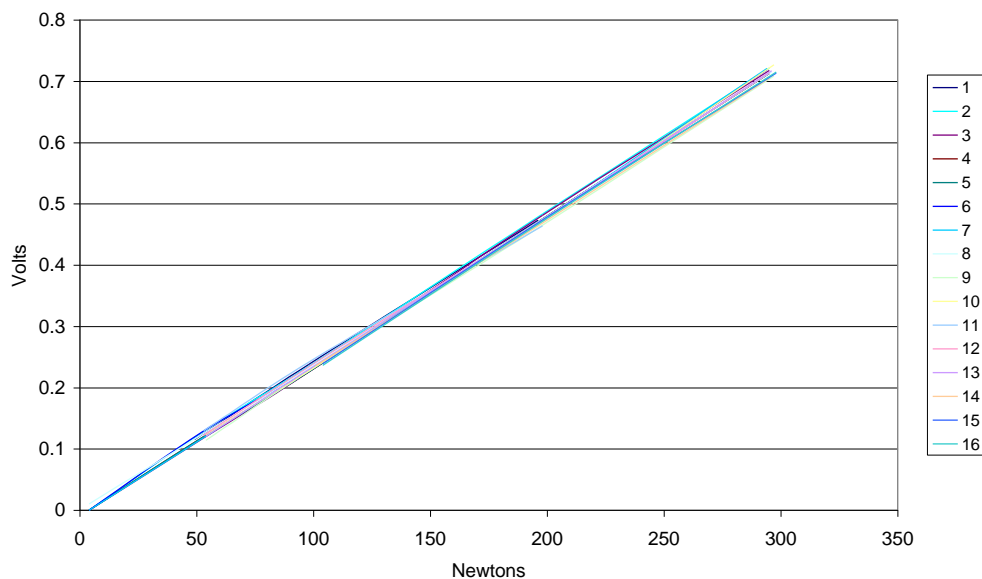
The Kin Com dynamometer lever arm was set at 0°, parallel to the floor. Known weights (5 Kg, 10 Kg, 20 Kg) were applied to the load cell attachment. Linear force readings were displayed in Volts using Signal software (version 2.13, Cambridge electronic design, UK). These measurements were repeated on 16 separate occasions over three months.

The linearity of repeated measurements over time and with increasing weights were examined using a line graph. The number of Volts per Newton at each weight was calculated for all repeated readings (48 values). The coefficient of variance and Pearson correlation coefficients between repeated readings were also calculated.

Results

The Kin Com demonstrated linearly increased force readings with increased weight. Sixteen repeated measurements are shown in Figure 3.

Figure 3 Repeated measurements of known weights on the Kin Com



One volt was found to equal a mean of 422.56 ± 12 Newtons.

The coefficient of variance was less than 3% (2.83%) and the Pearson's correlation between repeated readings was almost perfect ($r=0.999$). A limitation of this study was that heavier weights which more closely mimic knee extensor force could not be applied.

Appendix 6 The design of a potential exercise programme for people with peripheral neuropathies

Assessment

Medical tests should exclude cardiac or respiratory problems, including unmanaged autonomic dysfunction, which might worsen on exercise. Other assessments should identify potential risks of musculoskeletal injury including unsupported joints or compensatory movement patterns due to weakened muscles. Orthotic provision may be necessary to support joints at risk of damage during sustained activity.

Measurement of muscle strength using fixed dynamometry will identify weaker muscles which may be strengthened to facilitate aerobic exercise and function.

The level of functional aerobic fitness of the patient should be ascertained to provide a baseline level at which the programme can start. A conventional exercise test, using a cycle ergometer or treadmill, may provide indications of endurance and peak exercising heart rate to inform the exercise intervention. However, a test of this nature may be limited by factors other than aerobic fitness (e.g. muscle strength, perceived exertion) and may also exacerbate subjective fatigue, discouraging the participant. As an alternative, a functional exercise tolerance test, such as the six minute walk test, may also indicate peak exercising heart rate and provide qualitative data regarding exertion during functional exercise. Careful questioning may also provide information on current levels of exercise tolerance which will inform the design of the aerobic component of an exercise programme.

Outcome tools including the ONLS, mPCI, and Walk-12 which were evaluated and developed in this thesis could be used to assess activity limitations and mobility. Other instruments including the SF-36, FIS and HADS could also be used to indicate participation, subjective fatigue and mood.

Goal setting and progression

It is vital that the design of the exercise programme considers the aims and goals of the patient in order to promote adherence and compliance. The initial exercise sessions should also begin at an intensity level achievable by the participant.

Gradual increases in the duration and / or intensity of aerobic exercise (grading) are recommended for participants who cannot exercise for 20 minutes. Advice on pacing of exercise and rest could also help to limit fatigue and increase activity. This is particularly important for severely fatigued individuals. By minimising the exacerbation of fatigue related to exercise, adherence is also likely to be improved.

Compliance and adherence

Exercise should be unsupervised and based in the community to provide flexibility, increase adherence and to encourage participants to develop independent and long lasting health behaviours (Ashworth et al. 2005).

Participants should be informed about the normal feelings to be expected when exercising, including the mild muscle ache experienced by half of participants in the exercise study in Chapter Two.

Heart rate monitors could be used to provide feedback on the intensity of exercise whilst completing the aerobic component of the programme. In addition to providing feedback, heart rate monitors may reduce the focus upon feelings of exertion and effort (Moss-Morris et al. 2005). However, simple models should be used to avoid lost data as in Chapter Two.

Adherence to the programme can be judged by asking participants to note details of each exercise session in an exercise diary, by regular contact with the health professional and from the memory of heart rate monitors. If available, activity monitors (detailed in Chapter Five) could be worn throughout the initial weeks of the programme to ascertain adherence.

Exercise programme design

Frequency of exercise

Three exercise sessions should be completed every week to produce changes in fitness and strength. This is based upon recommendations by exercise authorities (American College of Sports Medicine 1995; Fletcher et al. 2001) and as this frequency was reported to be practical in the exercise study in this thesis.

Warm up

At the start of every exercise session, a ten minute warm up is recommended at approximately 60% of peak or age predicted heart rate (American College of Sports Medicine 1995). The duration of warm up may be gradually increased over successive exercise sessions if patients were initially unable to exercise for ten minutes.

Aerobic training

This should proceed directly from the warm up. Heart rates between 60 to 85% of peak heart rate should be reached during this component of the programme. If a baseline exercise test was not undertaken, maximum heart rate can be predicted from the age of the participant using (American College of Sports Medicine 1995):

Maximum heart rate (beats min^{-1}) = $220 - \text{age}$

The duration of aerobic exercise could be calculated from the level of exercise tolerance reported by the patient and from exercise testing. The duration of exercise should be increased slowly over successive exercise sessions, depending upon participant feedback and heart rate recordings.

Increases of one minute at each session have been used by others in fatigued participants (Fulcher and White 1997) and may be used in people with PN. If participants complain of worsening of fatigue symptoms, the duration of aerobic exercise should be maintained at the current level for one week, before continuing to progress (Fulcher and White 1997). The modality of training should be determined by the patient and physiotherapist to promote adherence whilst ensuring exercise is safe and effective. These modalities could include static cycling, walking or swimming.

Other exercises

Exercises to improve muscle performance should be included in the programme to strengthen weak muscles or if reduced muscular endurance appears to limit function or aerobic exercise (Brill et al. 2000; Clark et al. 1996). Ideally, these exercises should be completed directly after the aerobic component to eliminate the need for an additional warm up period. However, in participants for whom fatigue is problematic, the exercise programme could be paced so these exercises are undertaken after a period of rest and an additional warm up.

The number of sets and repetitions should be increased gradually, monitoring for signs of increased subjective fatigue and muscle ache. A maximum of three sets of ten repetitions appeared practical in people with PN in Chapter Two, and is recognised to provide an adequate strengthening stimulus (American College of Sports Medicine 1995; Galvao and Taaffe 2004; Wolfe et al. 2004). A limitation of the exercise study in Chapter Two was that participants only completed isometric contractions for reasons of safety. However, dynamic strength training is likely to have greater benefit to function, provide greater feedback to participants on progress and has been shown to increase strength in other studies (Lindeman et al. 1995; Ruhland 1997). However, as training is unsupervised, the health professional must be confident in the participant's ability to control a dynamic contraction throughout the range. Otherwise, isometric contractions could be used.

Functional exercises to improve posture, function and balance should be included to improve performance (de Vreede et al. 2005; Eng et al. 2003; Richardson et al. 2001). These should be informed by the findings of the initial assessment but may include postural and balance exercises.

Cool down

A five minute cool down is recommended to allow heart rate to return to resting levels (Fletcher et al. 2001). This should be followed by stretches of the major muscle groups exercised which may include quadriceps femoris, hamstrings and calf muscles.

Continuation of the programme

The exercise programme could be continued indefinitely. Regular re-measurement within the first months of exercise will guide the development of the exercise programme, identify problems and provide encouraging feedback for the participant. As the individual's ability to exercise increases, the health professional may advise the individual to begin other forms of exercise, and support return to, or uptake of specific leisure pursuits to maintain interest and

enjoyment. Contact with the health professional should become less frequent as the participant becomes more confident and familiar with exercise. However, intermittent follow up may be helpful to monitor progress and judge outcome. This can be agreed between the health professional and participant.

Appendix 7 Details of ethical approval of studies in this thesis

Study	Centre/Ethics committee	LREC/COREC number
Exercise in peripheral neuropathy	King's College London	01/02-135
	Guy's Hospital	02/05/14
An investigation of the inter-rater reliability of scores obtained on the ONLS measure from observation of patient ability	Guy's Hospital	03/02/10
	King's College Hospital	01-04-007
Investigation of reliability and validity of the PCI	King's College London	02/03/82
A study of fatigue in PN	King's College London	03/04-31
	Guy's Hospital	04/Q0704/14
Exercise and fatigue in PN	Bexley and Greenwich on behalf of South East London REC	05/Q0707/23

Appendix 8 Published papers

These papers were published under my maiden name of Graham.

Graham, R.C., Smith, N.S., White, C.M. The reliability and validity of the physiological cost index of walking in health participants when walking on two tracks Arch Phys Med Rehab 2005 Vol. 86, p. 2041-2046

Graham, R.C., Hughes, R.A.C. Clinimetric properties of a walking scale in peripheral neuropathy Journal of Neurol Neurosurg Psychiatry 2006 Vol. 77, p 977-979

Graham, R.C., Hughes, R.A.C. A modified peripheral neuropathy scale: the overall neuropathy limitations scale. J Neurol Neurosurg Psychiatry 2006 Vol. 77, p 973-976

Graham, R.C., Hughes, R.A.C., White, C.M. A prospective study of physiotherapist prescribed community based exercise in inflammatory peripheral neuropathy J Neurol. 2007 Vol. 254 p 228-235

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